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* Compared to a standard nutritional drink.

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Endocrinology: more than just a sliding scale

The study of hormones is one of the more nascent and elusive branches of medicine. The idea that invisible chemicals released from diminutive glands can cause darkening of the skin, racing metabolism, and growth of gigantic proportions is as mystifying to the lay patient as it is to most physicians.

The general public confusion about what endocrinology entails became apparent to me on several clinical rotations. During a paediatric endocrinology consult for a child with short stature, the mother inquired about her daughter's diabetes. When I expressed surprise that the child was diabetic, she replied that she was not, but assumed that this was the role of an endocrinology consult. As diabetes comprises a substantial portion of the endocrinology practice, many lay people assume that this condition and subspecialty are interchangeable. As further illustration, an elderly patient informed me that she regularly saw her "bone doctor." She was unfamiliar with the term endocrinology; her understanding of the person who treated her osteoporosis was that she was a bone specialist.

The public confusion about the practice of endocrinology is understandable if one considers the history of the subspecialty. The word "hormone" was not conceived until 1905, when Starling described "the chemical messengers, which speeding from cell to cell along the bloodstream, may coordinate the activities and growth of different parts of the body." As early as Hippocrates (400s BC), physicians had an idea that certain glands could produce surprising effects on the entire body. However, the thymus gland was not discovered until the time of the Alexandrians (300s BC); the pituitary, pineal, and thyroid glands were noted by Galen in 170 AD; Eustachi discovered the adrenals in the 1500s; Langerhans found the pancreatic islets in 1869, and the parathyroids were unknown until the work of Sandstrom in 1880. It is thus unsurprising that the field of endocrinology is one of the more unfamiliar subspecialties as the glands that control this system had only been described 130 years ago. In comparison to a field such as cardiology, whose organ and effects have had the benefit of centuries of study, endocrinology is only beginning to be unravelled.

As a medical subspecialty, endocrinology began to gain recognition in North America in 1916 when the Society of Internal Secretions was formed. Today, The Endocrine Society (USA) and The Society of Endocrinology (UK) are two of the main governing bodies. These organizations have recognized the confusion that the concepts of hormones and endocrinology can produce and have designed websites to educate the public. Our role as physicians is to do the same.

One of the keys to compliance with therapy and a strong doctor-patient relationship is patient understanding. If our patients do not understand what the pituitary gland is, where it is located, and what effects it has, they are unlikely to be satisfied with a diagnosis of pituitary dysfunction, nor will they have confidence in our proffered therapies. One of the central roles of the endocrinologist is thus that of educator.

Familiarity with the field of endocrinology is necessary not only for budding hormone specialists, but for all physicians. A common ward misconception is that the endocrinology consult service exists to manage the insulin sliding scale. Our patients will be better served by an understanding that hormones play a role in every organ system, in every disease, in every patient. The Endocrine Society has summarized this central role of endocrinology in their Strategic Plan—Vision for the Field of Endocrinology:

"Endocrinology will be widely accepted as the fundamental science of molecular, cellular, and systems communication that underpins human health and disease. It will be recognized as an interdisciplinary scientific and clinical specialty that integrates basic and clinical research with patient care. It will define the ways in which the body's communication systems signal organ coordination, function and dysfunction." 

This issue of the UWOMJ is dedicated to the stimulating field of endocrinology. The feature and departmental articles in this issue display the breadth of issues and challenges encountered in an endocrinology practice.

As in clinical practice, the topic of diabetes remains a major focus of articles in this issue. Commonly-presenting scenarios, such as the evidence for blood glucose self-monitoring, diagnosis of metabolic syndrome, diabetes associations with coronary artery disease and managing laboratory values and side effects of common medications taken by those with diabetes will help consolidate our knowledge in the area. These articles are published alongside more uncommon issues in diabetes management, such as cystic fibrosis-related diabetes, 'diabulimia,' and how urban planning influences diabetes.

There are many current 'hot topics' within the domains of endocrinology. This issue's articles on bioidentical hormone therapy, bariatric surgery, drug doping and gender testing in athletes shed light on current developments and may help us better educate our patients on the evidence behind the often-sensationalized media stories.
We wish to extend a large thank you to the departmental editors, feature article writers and faculty reviewers for their commitment to educating others about endocrinology. Special thanks to Pencilla Lang, Ed Weiss, and Pat Montaleone, for their tireless work in overseeing the compilation, layout, print and online publication, awards and finances for the journal. Enjoy!

Tiffany Kwok          Laura Hinz
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References


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Endocrinology: more than just a sliding scale
Bariatric surgery: Lots to lose, much to gain

Edward S. Weiss (Meds 2012) and Sandeep Dhaliwal (Meds 2013)
Faculty reviewer: Dr. Andreana Büttier, Department of Surgery, UWO

Introduction

The treatment of obesity has long been considered to fall under the rubric of "lifestyle modification," with diet and exercise making up a large part of the prescription to the patient seeking to lose extra pounds. Unfortunately, it has been shown that behavioural modification has only a modest effect on long-term maintenance of weight loss, with the average dieter losing less than 5kg with diet and exercise alone.1

In recent years, it has become increasingly clear that more aggressive therapy may be a superior option to treat obesity, especially when overweight and its sequelae preclude the pursuit of exercise, or when the behavioural milieu is such that modification is unlikely to succeed. While pharmacological treatment of obesity has shown some limited success,2 it is bariatric surgery that appears, at this time, to offer obese people the highest probability of drastic and permanent weight loss, with its attendant benefits on physical, as well as emotional health.

Types of bariatric surgery

Surgical interventions for the obese are not new, having been mentioned by early sources such as the Talmud (circa 500 CE) and the Greek historian Claudius Aelian (circa 200 CE).3 However, the modern age of bariatric surgery began in the 1950s, when surgeons at the University of Minnesota began removing variable lengths of small bowel to try to reduce the absorption of food in obese patients. The untoward side effects of this procedure - diarrhea, micronutrient deficiencies, kidney stones, polyarthritis, and even cirrhosis4 - led to experimentation with alternate surgical strategies. In the 1960s, surgeons attempted gastric bypass, based on the observation that patients who underwent partial gastrectomy for the treatment of peptic ulcers were unable to gain significant weight following their operations.5 In this procedure, the stomach was asymmetrically split, with only a small upper pouch remaining in continuity with the small bowel. Patients found that the reduced size of their stomachs caused them to become satiated early, with overconsumption becoming particularly unpleasant.

These early procedures are, respectively, representative of the two primary strategies in bariatric surgery: malabsorptive procedures, which aim to lower the rate of absorption of calories consumed; and restrictive procedures, which aim to limit the actual intake of food by provoking early satiety. Further refinement has led to three different procedures which are now commonly performed as a method of treating obesity (Figure 1).

Adjustable gastric banding

Gastric banding was introduced as a bariatric procedure in the late 1970s. In its first incarnation, the gastric band was a non-adjustable plastic mesh applied circumferentially around the upper portion of the stomach, creating a small pouch which restricted overconsumption. Refinement in the years following led to the creation of the adjustable gastric band (AGB), which consists of a hollow silicone ring connected by a narrow tube to a subcutaneous access port. In this manner, the size of the upper stomach pouch can be adjusted by the infusion of saline through the port and into the band. If, for example, the rate of weight loss is deemed to be too slow, the band can be tightened and the pouch made smaller. Conversely, if a patient with a gastric band were to become pregnant and require a higher caloric intake, the band can be loosened by removing fluid.

There are several relative benefits to AGB. Although performed laparoscopically like most modern bariatric operations, band placement is relatively less invasive. It involves no staples, transections, or anastomoses, and is thus associated with the lowest rates of post-operative complications and mortality compared to other procedures.6 Weight loss is more gradual than with more invasive malabsorptive procedures, but the percentage of excess weight lost has been found to be similar in some long-term studies.8 The adjustability of the band and the potential for easy reversibility are additional factors that make the gastric band an attractive choice.

Although major complications from gastric banding are quite rare, there are, nonetheless, some drawbacks to the procedure. Studies have reported unwanted pouch enlargement as a complication in 10-15% of patients, as
well as band slippage and distal stomach prolapse in 2-4%; these often necessitate reoperation or band removal. Additionally, it has been found that in patients classified as "super-obese" (BMI > 50), weight loss and improvement in comorbidities such as type 2 diabetes are superior in other types of procedures.

Vertical sleeve gastrectomy

Vertical sleeve gastrectomy (VSG) evolved in the milieu of increasing recognition of the effectiveness of restrictive procedures, combined with the rapid adoption of automated surgical staplers in the 1970s. In this procedure, the fundus and greater curvature of the stomach are removed through vertical stapled resection, resulting in a tubular or banana-shaped sleeve with a volume of around 15% of the original stomach. Although purely restrictive in intent, it is thought that lower circulating levels of ghrelin, a hunger-inducing hormone produced in the gastric fundus, may contribute to the weight loss seen by patients.

The benefits of VSG are similar to those of other restrictive procedures. Although long-term results have not yet been published, studies suggest that short-term weight loss is comparable or superior to that of patients who have undergone gastric banding. The procedure also spares the absorptive function of the small bowel, although it is recognized that there is a potential for impaired vitamin B12 absorption due to the lack of intrinsic factor production. Technically, a partial gastrectomy is simpler than many of the malabsorptive procedures, and it can also be converted to a gastric bypass in the event of failure to lose weight. However, it appears that more long-term results will be required before VSG is a standard part of the bariatric repertoire.

Roux-en-Y gastric bypass

The Roux-en-Y gastric bypass (RYGB) is widely becoming one of the most popular surgical options for weight loss. A technically complex procedure, it involves the creation of a small restrictive stomach pouch, but additionally reconstructs the small bowel to promote a malabsorptive state. In the traditional procedure, the jejunum is transected approximately 50cm distal to the ligament of Treitz. The distal limb of the jejunum is anastomosed to the reduced upper stomach pouch, while the proximal limb, which transmits bile and pancreatic secretions from the duodenum, is anastomosed approximately a meter down the distal limb. Unlike a sleeve gastrectomy, an RYGB leaves the rest of the stomach in situ, making the operation potentially reversible if necessary.

Weight loss stimulated by RYGB has been found in some studies to be superior to that of purely restrictive procedures, and health-related quality of life has also been shown to be significantly better. This benefit over other procedures has been attributed partially to the malabsorptive state, but also to changes in taste preference and the aversive sequelae of the dumping syndrome, which is an unpleasant combination of gastrointestinal and vasovagal disturbances that often results from the ingestion of sugar-laden meals following gastric bypass. Furthermore, the exact extent of intestinal bypass can be adjusted in order to promote ever further weight loss, though this does run the risk of developing micronutritional deficiencies.

Complications following RYGB are, as expected, somewhat higher than with purely restrictive procedures. However, operative mortality has been reported to be less than 1%, and the primary complications are related to malabsorption of vitamin B12 and iron; these can be easily corrected with supplementation.

Benefits of bariatric surgery

There is little doubt that bariatric surgery is effective for weight loss. A meta-analysis looked at the outcomes of 22,000 patients who underwent some sort of bariatric surgery, and found that the average loss of excess weight was 61.2%. The study also reported that the majority of patients also experienced a resolution of pre-existing type 2 diabetes, hypertension, hyperlipidemia, and obstructive sleep apnea. Operative mortality was, on average, less than 1%, which is deemed to be much lower than the risk of premature mortality from the health consequences of obesity.

Aside from the physical health benefits of bariatric surgery, it appears that treatment can also have a substantial impact on emotional and mental health as well. Numerous studies have shown that people living with obesity have significantly higher rates of mood and anxiety disorders, as well as decreased self-esteem and self-acceptance. Successful weight loss following bariatric surgery often results in improvement in these domains as well.

While at first glance it may appear that surgical management of obesity has the disadvantage of being relatively expensive, several studies have borne out the assumption that the increased expense in the short term is, in fact, less costly than the medical management of severe obesity and its comorbidities, which can often amount to $10,000 per patient per year or more in Ontario. Additionally, it has been found that obese patients who undergo bariatric surgery are more likely to be employed and not dependent on social welfare support compared to before their surgeries, which only furthers the case for surgery in the very obese.

Access to bariatric surgery

With the alarming reminders of the growing "obesity pandemic" forefront in the public mind, and the growing awareness of bariatric surgery as an effective treatment option, it is not surprising that demand for surgical treatment is far higher than the available supply in Canada. A recent study that polled Canadian bariatric surgeons found that the average wait time for publicly-funded procedures performed locally is around five years. In response to the extreme demand, provincial governments have been increasingly funding bariatric surgery performed out-of-province and out-of-country. Ontario, for example, funded over 1,500 out-of-country procedures in 2008-2009, at a cost that far exceeds
the comparable cost in Canada.\textsuperscript{20} Meanwhile, those with suitable financial means often take advantage of privately-run clinics, which offer procedures not funded by provincial health plans. Gastric banding, for example, is available at a cost of around $16,000, with wait times in the range of weeks to several months. Others, seeking a less-expensive alternative, have been known to travel to Mexico and India, where the procedures can be done in short order at a fraction of the Canadian price.

Perhaps in recognition of the dire situation surrounding the inequity of access to bariatric surgery, several provincial governments have announced new funding strategies to increase access to weight loss procedures. Ontario is investing $75 million to increase its bariatric surgical capacity by nine-fold in the next few years,\textsuperscript{20} and Quebec intends to shorten waiting times to six months through a significant infusion of new funds.\textsuperscript{21} These sorely-needed expansions are expected to make a vast difference in the morbidity and mortality of those suffering from severe obesity.

**Conclusion**

In the absence of effective primary prevention, bariatric surgery appears to be the most promising treatment option for obesity and its resultant comorbidities. While the optimal surgical approach has yet to be decided, it is clear that procedures for weight loss will continue to evolve in order to maximize benefit and reduce the risk of complications. Inequitable access to these procedures represents a major barrier to successful treatment of severe obesity on a population level, but the recognition by provincial funding agencies that these treatments are beneficial is leading to positive change and an overall increase in the well-being of Canadians suffering from obesity.

**References**

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Metabolic syndrome

Julie Huang (Meds 2012) and Jai Jayakar (Meds 2013)
Faculty reviewer: Dr. Terri Paul, Department of Medicine, UWO

Introduction

Metabolic syndrome (MetS) is a common disorder characterized by the clustering of risk factors for developing cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM). Though the idea of MetS has existed for over 80 years, the concept was not further developed until 1988; since then our understanding of this disorder has been continuously evolving. The precise definition and criteria for diagnosis of MetS has been rapidly changing in recent years.1·3

The signs that characterize MetS include central obesity, dyslipidemia, hyperglycemia and hypertension. It is believed that the diagnosis of MetS is a greater predictor for the development of CVD and T2DM than the consideration of these risk factors independently.4 In keeping with its classification as a ‘syndrome,’ there has not been a single cause identified in the etiology of MetS, and there is still much that is unknown about its pathophysiology. Indeed, it is even unclear whether MetS is a ‘true’ syndrome where the symptoms are related by pathophysiology, or whether the disorder is simply a collection of common independent risk factors from differing disease phenotypes.4 Nevertheless, insulin resistance is the most commonly accepted mechanism through which MetS develops.5

There have been many definitions of MetS released by separate institutions since the WHO released the first formalized criteria in 1999. Each of the criteria considers similar parameters that reflect both our understanding in the pathophysiology of MetS, as well as the clinical presentation of the disorder. There are differences between guidelines in cutoff values and the combinations of symptoms that will allow a diagnosis. This article will review three guidelines – the WHO, ATPIII and the IDF – as these appear to be the most commonly used criteria in the current literature.

Current guidelines – review and comparison

The specific details of the criteria are summarized in Table 1 for comparison. The first set of diagnostic criteria was put forth by the WHO diabetes group in 1999. Insulin resistance or impaired glucose tolerance or diabetes, hypertension, dyslipidemia, obesity and microalbuminuria were defined as the components of MetS.5 These criteria were felt to be difficult to measure in the clinic; the oral glucose tolerance test and albumin measurement were not feasible tests that could be easily done in the clinic. In response, the US National Cholesterol Education Program: Adult Treatment Panel III (NCEP-ATP III or ATPIII) in 2001 released a new set of criteria where insulin resistance was measured by a fasting glucose test, a simpler test than the oral glucose tolerance test. The combination of risk factors and cut-off levels also differed from the WHO criteria. The ATPIII criteria, however, still had their shortcomings. Although easier to use in the clinic, the ATPIII guidelines were not suitable for an international population; for example, ethnic differences in BMI were not addressed.

In 2004, in order to clear the confusion between multiple guidelines and to create an internationally applicable guideline, the International Diabetes Federation released a unified definition in 2005 (updated in 2006).6 Like the ATPIII, the IDF used criteria that could be easily tested in the clinic. The most significant change in the IDF criteria was the use of central obesity as a necessary component for diagnosis. Also important was the attempt to make the criteria applicable for a worldwide population by releasing cut-off levels for central obesity that were specific for different ethnicities. The cutoff values were generally lower than levels present in the other criteria, and the specific values were obtained using anthropometric studies of different populations.7

In addition to the three guidelines that have been outlined, it is important to note other guidelines released by institutions such as the American Association of Endocrinology, the National Heart, Lung, and Blood Institute (NHLBI). These are all similar, but differ slightly in cutoff levels.

Prevalence and predictive value

MetS is a very common disorder. The literature suggests a prevalence ranging from 14-32%.3,6·7 Specific prevalence depends on geographic location, population characteristics such as ethnicity, and the criteria used to define MetS. The majority of studies suggest that a higher prevalence of MetS is identified using the IDF criteria than the ATPIII criteria.6·7

The importance of MetS lies in its ability to predict more significant disease, primarily T2DM and CVD. While there is strong evidence to suggest that MetS is a good predictor of T2DM, the ability to predict CVD in MetS is controversial.6 In addition to T2DM and CVD there have also been studies suggesting that MetS can predict other diseases and outcomes, including chronic kidney disease, sexual dysfunction, hypogonadism, polycystic ovarian ovarian syndrome (PCOS), fatty liver and all-cause mortality.8·11

The literature suggests that MetS is a strong predictor of developing T2DM. The specific predictive ability differs between different studies and between criteria. A number of separate studies have compared the ability of the ATPIII criteria and the IDF criteria in predicting diabetes in different populations. In the articles reviewed, the predictive value of MetS ranges, with articles listing an increased RR of 3.08 all the way to 10.10.7·11·12·13 Comparing sets of
Metabolic syndrome

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<thead>
<tr>
<th>WHO</th>
<th>ATP III</th>
<th>IDF</th>
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<tbody>
<tr>
<td>Impaired glucose tolerance or insulin resistance or a diagnosis of T2DM</td>
<td>Any three or more of the following:</td>
<td>Central obesity w/ ethnic specific values or BMI&gt;30</td>
</tr>
<tr>
<td>Plus any two of the following:</td>
<td>Raised Triglycerides ≥ 1.7 mmol/L</td>
<td>Raised Triglycerides ≥ 1.7 mmol/L</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>Reduced HDL cholesterol &lt; 1.03 mmol/L (males)</td>
<td>Reduced HDL cholesterol &lt; 1.03 mmol/L (males)</td>
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<tr>
<td>Triglycerides ≥ 1.7 mmol/L or HDL &lt; 0.9 mmol/L (males) or HDL &lt; 1.0 mmol/L (females)</td>
<td>&lt; 1.29 mmol/L (females)</td>
<td>&lt; 1.29 mmol/L (females)</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>Hypertension ≥ 130 systolic or ≥ 85 diastolic (mmHg)</td>
<td>Hypertension ≥ 130 systolic or ≥ 85 diastolic (mmHg)</td>
</tr>
<tr>
<td>Albumin excretion &gt; 20µg/min</td>
<td>Raised fasting plasma glucose</td>
<td>Raised fasting plasma glucose ≥100mg/dL or previously diagnosed T2DM</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Central Obesity &gt;102 cm (male), &gt;88cm (female)</td>
<td></td>
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<tr>
<td>&gt;140/90 mmHg</td>
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<td></td>
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<tr>
<td>Obesity</td>
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<tr>
<td>BMI &gt; 30 or waist:hip ratio &gt; 0.9 in males, &gt;0.85 in females</td>
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Table 1. Summary of the WHO, ATPIII and IDF criteria for metabolic syndrome

Discussion

MetS identifies individuals that are at risk of developing CVD and T2DM, but its ability to do so is confounded by the existence of multiple criteria, and a lack of knowledge of this disorder. A formal definition of MetS was created only in the last 10 years, and there have been few long-term studies on MetS. The resulting lack of evidence and an incomplete knowledge of its pathophysiology are also significant sources of confusion. While MetS is able to predict diabetes and CVD to an extent, its efficiency and effectiveness are controversial. For instance, the IDF criteria has been criticized for missing high risk patients that do not show central obesity. The ability of MetS to predict disease has been shown to be no more effective than existing methods. Other studies suggest that the risk associated with MetS is no greater than the risk associated with its individual components. This brings into question the clinical value of diagnosing MetS.

Nevertheless, there is convincing evidence for the use of MetS. Recently, a report has been published supporting the use of MetS as an important public health tool. It acknowledges the limitations that MetS has in predicting DM and CVD, but it also stresses that combined with other clinical tools and other existing guidelines, MetS can be useful in helping patients understand their level of risk and its potential impact on their health in the future. Underlining how separate risk factors can be interrelated can have an important role in helping both clinicians and patients address risk factors, especially if lifestyle modification is the goal.

Recent research has been focused on addressing the limitations and confusion that surrounds MetS. Most recently, in October, the IDF and AHA have jointly released a new guideline that attempts to unify the MetS criteria. Other areas of recent research include establishing more evidence to better refine the MetS criteria, with a particular focus in different subpopulation and ethnic groups. With the incidence of childhood T2DM on the rise, there is a need to develop standardized criteria for MetS diagnosis in the pediatric population.

In summary, MetS is a useful tool to identify individuals at risk for developing T2DM and CV. There are many
issues that limit its clinical value, including confusion between the existence of multiple guidelines, controversy in the research, lack of evidence, and a poor understanding of its pathophysiology. Nevertheless, it is important to appreciate the function of MetS, especially as the incidence of CVD and T2DM continues to rise in today's society.

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Addressing the new teen trend of “diabulimia”: Moral quandaries of a pediatric endocrinologist

Julie Hughes (Meds 2012)
Faculty reviewer: Dr. Louis C. Charland, Departments of Psychiatry and Philosophy, UWO

The management of diabetes mellitus in adolescents has grown increasingly nuanced as insulin resistance appears at ever-younger ages and technology advances into hitherto unattainable realms. Hence, it is in the midst of an already complex milieu that a new syndrome has managed to emerge largely unnoticed. This rarely researched and thus largely mysterious condition has been dubbed “diabulimia” by the media; the scientific community has yet to name it. Diabulimia refers to the practice of withholding insulin in order to lose weight. It typically co-exists with other disordered eating behaviour (DEB; e.g., extreme restriction, use of laxatives, etc.) or full-scale eating disorders. DEB is particularly worrisome in the context of pediatric diabetes for two reasons:

(a) It is dangerous. Eating disorders in diabetics are associated with poor metabolic control, greater need for hospitalization, a higher rate of microvascular complications (in particular retinopathy and nephropathy), and premature mortality.

(b) It is common. A startling 51% of adolescents in a Toronto study reported DEB, and over 10% met diagnostic criteria for an eating disorder. The root of this rather extraordinarily high prevalence is unknown, but there have been postulations: diabetic children are encouraged to pay a great deal of attention to their diets and also tend to have higher BMIs than their peers, which may increase anxiety about weight. The problem seems to increase with age: deliberate insulin omission is reported by roughly 2% of preteens, 15% of mid-teens, and 30-39% of older teens.

The remainder of this paper will focus on ethical concerns that may arise in the care of these patients. As Carney insightfully notes, “Behavioural disorders accompanied by questionable beliefs... expose the frailties of medico-legal knowledge.” If we attempt to understand these frailties and grapple with those issues for which “there is no ‘right’ decision, only a decision that is thoughtfully made and perhaps ‘more right’ than the alternatives,” we will gradually strengthen the ethical foundations on which medicine relies.

Case 1

You receive an urgent page informing you that Erica, a 15-year-old patient of yours, is in diabetic ketoacidosis at the hospital. You go to see her and discover that she has been skipping many of her insulin doses for months and does not wish to be treated for her ketoacidosis with insulin. She is terrified at the prospect of gaining weight and equates taking insulin with weight gain and loss of control. What should you do?

Though literature on diabulimia is scant, much has been written on the ethics of compulsory treatment for anorexia nervosa, and the essential difficulty in both circumstances is the same. It lies in balancing two of the most sacredly held principles of bioethics: beneficence and autonomy. Put in another fashion, this is a tension between positive rights (i.e., the right to health) and negative rights (i.e., the right not to be hospitalized or treated against one’s will).

Before moving on any further, it is crucial to get the question straight. In this case, there is in fact more than one question. The first is this: should a clinician respect a competent patient’s autonomy if his or her own vision of the patient’s best interests differs from the patient’s (assuming that what the patient desires the clinician to do lies within ethical bounds)? That question has been considered in depth and resolved. It is not a very difficult one when well-being is considered from a holistic point of view, since “a respect for autonomy clearly emerges from a beneficence-based ethic.” In the case of eating disorders, however, we have a cluster of more complicated questions, ones in which beneficence and autonomy truly do conflict: they are questions regarding the nature of competence, how mental illness can affect it, and what to do when it is fragile or absent.

Competence requires the ability to understand and remember information about treatment options, appreciate the personal reality of relevant benefits and risks, weigh and consider various possibilities, and express a choice. While an eating disorder certainly does not automatically remove a patient’s capacity to make medical decisions, concern is valid and needs to be explored on a person-by-person and task-by-task basis. Anorexia, the most studied of the eating disorders, has variable and unpredictable effects on concentration, beliefs, and information processing. Patients frequently express contradictory convictions: for example, they usually do not want to die, yet they also do not want to eat enough to live. Whether these difficulties are of a nature that can be adequately captured on standard tests of competence (e.g., the MacCAT-T) is a matter of debate. Some propose that pathological values derived from the eating disorder may cause a cognitive impairment greater than that detected by current tests.

The extent to which the cognitive distortions of
anorexia are present in diabulimia is unknown and difficult to surmise, since both severe malnutrition (which may or may not be present in diabulimia) and the mental illness itself contribute to them. The latter should not be underestimated, for "the types and range of relationships that patients may have with the eating disorder are similar to the relationships they may have with people". Thus, establishing the competency of a patient with any eating disorder requires a careful and thoughtful evaluation. In Ontario, a hearing before the Consent and Capacity Review Board is sometimes necessary, though this is impractical when urgent care is required.

If it is determined that a patient is not competent to refuse a specific medical intervention, the treatment team must then discuss the issue with a substitute decision maker (in pediatrics, usually the parents) and offer appropriate counsel. For patients who do not have an advance directive, the guiding standard generally applied is that of "best interests". This raises a new question: even with legal permission, is it good judgment to treat Erica against her will? Forced treatments are highly psychologically distressing and may jeopardize recovery if used excessively. All costs must be counted and the patient's wishes should be respected whenever possible, even if he or she is not competent.

Nonetheless, in Erica's case, we suggest that the standard of best interests would involve administering insulin. There is good rationale, indeed probably better rationale than for forced feeding in anorexia: she is in an acutely life-threatening situation, the intervention is of known medical benefit, there are no viable alternatives, and her true wishes cannot be reliably ascertained due to the cognitive effects of her illness. Further, because an eating disorder is normally an expression of emotional distress rather than a genuine attempt at a slow suicide, there is a particularly strong duty to protect. This scenario is not akin to withdrawing care at end-of-life; patients with eating disorders do recover and frequently go on to lead full, happy lives.

It goes without saying that Erica will need other care. Her ability to consent to (or refuse) each intervention should be considered independently by a clinician attuned to possible changes over time. The process of evaluating competence can be given more thought and time once she is stable. Fortunately, compulsory treatment given sensitively does not seem to negatively affect the therapeutic relationship.

Conceptually, perhaps the most important point here is that the underlying rationale is not a lack of respect for autonomy but a belief that true autonomy is occasionally impossible. Hence, the goal is not to privilege the clinician's view over the patient's, but to give what the patient's genuine self, rather than her mentally ill self, would want, with the ever-present hope that in the future she will regain the ability to choose freely and even healthfully. Clinicians should strive for the model achieved in a British Columbia eating disorders program in which "the team is always working towards empowering the patient to achieve her own agency and at the same time must remain cognizant of the power of the anorexia, which may mask the authentic wishes of the patient to seek wellness." A blind and unconscionable adherence to the wishes of a patient who is in severe psychiatric distress and desperate medical need helps no one.

Case 2

You head back to your office. Laura, a 12-year-old with Type 1 diabetes, is coming to see you for a routine check-up. Upon reviewing her chart, you discover that her sugar levels are rather high and she has lost about 10 pounds. What is your approach?

This particular scenario is not ethically complex, yet it is important, because if you were to discover that Laura has a full-scale eating disorder, you would have a window of opportunity to simultaneously avert suffering and avoid the ethical complexities of the previous case. Call it "preventative ethics", if you will. You might accomplish these goals by (a) treating her early, and (b) working with Laura, her family, and an interdisciplinary team to prepare an "advance directive" that could be used to guide treatment if she should lack decision-making capacity in the future. Evidence suggests that DEB persists for at least five years in over 90% of cases; a "wait-and-see" approach is not wise.

Unfortunately, physicians feel that they lack training in caring for adolescents with these difficulties, and routine care is likely inadequate. Recommendations for those hoping to achieve successful early intervention include yearly screening questions beginning in the preteen years, attempts to normalize eating behaviour and bolster self esteem early in the course of illness, and a low threshold for referral to specialized eating disorder services. Last but never least, according to patients, the "key to a meaningful intervention is to be recognised by the therapist as a person".

In sum, "diabulimia" illuminates the ethical importance of early intervention in mental illness and raises important moral issues that the field of pediatric endocrinology will need to address in coming years. Such discussion is an integral part of the rapid evolution of society and medicine, for as Macdonald so aptly put it, "Ethics - the making of value judgments, of weighing our actions against shared standards - is a task inherent to clinical life."

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Self-monitoring of blood glucose for type 2 diabetes mellitus patients

Jenny Shu (Meds 2012) and Paul Kudlow (Meds 2013)
Faculty reviewer: Dr. Ruth McManus, Department of Medicine, UWO

Introduction

Among the many rising global health epidemics, diabetes mellitus can be argued to be one of the most concerning ones with over 246 million people affected worldwide currently and 380 million people expected by 2025. Type 2 diabetes mellitus (T2DM), or non-insulin dependent diabetes, accounts for 95% of all cases of diabetes and results in significant morbidity and long-term complications affecting multiple organ systems, such as microvascular pathology in the retina, peripheral neuropathy, nephropathy, and most importantly, macrovascular disease affecting arteries supplying the heart, brain, and lower extremities. In fact, the risk of developing cardiovascular complications in T2DM is two- to fourfold higher for men and women respectively, relative to a non-diabetic population.

Tight blood glucose control is one of the pillars of patient-centred self-management, but the role for testing glucose levels in order to achieve tight control has been met with many challenges and debate. Technology that allows for self-monitoring of blood glucose levels has only been commercially viable since the early 1980’s. While there has been evidence to suggest the benefit of using self-monitoring of blood glucose (SMBG) for diabetic individuals on insulin (patients with either T1DM or T2DM on insulin), there has been limited research and controversy on whether the high personal and financial cost burden of SMBG is beneficial for most non-insulin dependent T2DM patients. This article will explore the challenges and gaps of knowledge in using SMBG for the management of patients with T2DM, as well as identify recommendations and improvements that can be made to aid patients in their disease management.

Current evidence

The current clinical evidence supporting the use of SMBG on improving the outcomes of non-insulin dependent T2DM patients is controversial and inconclusive. Most published trials of SMBG use the glycosylated hemoglobin (A1C) (HbA1C) levels as a surrogate marker for overall glycemic control and risk of secondary complications, but the methods utilized with respect to the intervention (e.g. frequency of SBGM, follow-up, and education) have been heterogeneous and hence difficult to generalize.

A recent key study conducted by the DiGEM (Diabetes Glycemic Education and Monitoring) Trial Group used an open, parallel group randomized control trial methodology. It was concluded that there was no convincing evidence to recommend routine SMBG for all T2DM patients, nor any evidence of improved glycemic control relative to usual care monitored by HbA1C levels.

However, in contrast, a meta-analysis conducted by Jansen et al. looking at 13 randomized controlled trials was able to report conclude that SMBG improved the HbA1C by more than 0.40% and this reduction nearly doubled after providing medical feedback. Similarly, Towfigh et al. concluded from their meta-analysis of 9 randomized control trials that T2DM patients not on insulin using SMBG had a statistically significant although modest improvement in glycemic control relative to those without SBMG.

Moreover, a study by McGeoch et al. suggested that there may be a subset of T2DM patients who benefit from SMBG. Specifically, they conducted a systemic review of 3 randomized trials and 13 observational studies published since 1990. Based on results from a patient group managed with oral hypoglycemic agents and/or diet alone, their conclusion was that only larger studies with a higher initial HbA1C of > 8% showed improvement in glycemic control with SMBG.

Challenges and Limitations

It has been difficult to consolidate data and compare research on SMBG in T2DM patients due to inconsistency of outcome measures, as well as a lack of using other measures beyond the HbA1C value to monitor efficacy. Welschen et al. suggest that additional factors such as quality of life, wellbeing, patient satisfaction, and hypoglycemic episodes should also be comprehensively incorporated into the outcome measures.

Another limitation of the current literature is that many studies have not reported use of a validated or standardized algorithm for patients to implement changes in therapy. For example, in the Juvenile Diabetes Research Foundation study, patients were instructed to calculate their insulin dose and adjust it according to their blood glucose levels according to standardized protocols. Use of such protocols not only allows for more consistency by reducing confounding factors affecting the outcome measures, but also helps to encourage patient self-education and interpretation around SMBG. Accordingly, both education and ongoing support have been cited as areas requiring further development in adopting a SMBG intervention for T2DM patients who need more guidance on the course of action when observing a high blood glucose level. In fact, patients with chronic hyperglycemia may develop increased anxiety, feel more burdened with their health care, and even perform inappropriate actions if they do not possess an adequate understanding of normal fluctuations of blood glucose.

Recommendations

While there has been a lack of consensus on whether to adopt SMBG as part of routine care for all T2DM patients,
there has been some agreement that certain subpopulations may benefit from regular SMBG. Specifically, tight glycemic control is very important during pregnancy as preventing fetal malformation, stillbirth, neonatal hypoglycemia, and respiratory distress.\textsuperscript{13} Furthermore, changes in HbA1C levels are too slow and retrospective to be used as an accurate measure of glycemic control during this sensitive time period.\textsuperscript{14} Similar parallels can be drawn with other special circumstances such as new diagnosis of T2DM, initiation or change in medication, or concurrent illnesses where SMBG may prove to be of benefit.\textsuperscript{9}

Given that a goal of SMBG is to promote self-management skills in the T2DM patient, identification of behavioural and personal characteristics which may predispose a patient to maximally benefit from SMBG would likely result in improved and long-term outcomes. For instance, “ideal” patients have been identified as those who know how to take a reading, interpret the reading relative to target values, formulate a connection between deviant readings and prior behaviour, create and implement action plans, and evaluate glucose readings in a non-judgmental framework.\textsuperscript{15}

Conclusion and Future

Tight glycemic control is an important goal of self-management in T2DM in order to prevent secondary complications. While there has been evidence supporting the use of SMBG for insulin-dependent diabetes, most research studies lack sufficient consistency and homogeneity in methodology, clinical follow-up, and patient populations to make a conclusive recommendation for its use in the routine daily management of T2DM patients.

Future areas for productive research in this area include developing more educational and ongoing support for T2DM patients to improve understanding of blood glucose readings and their associated clinical implications. Also, defining other relevant outcomes for SMBG beyond the A1C would be relevant. There may be subpopulations of T2DM patients who would benefit more from SMBG due to their need for tighter glycemic control during special circumstances, such as during pregnancy, new diagnosis, a change of medications, or other co-morbidities. Despite the current challenges with consolidating evidence on the benefits of SMBG for the T2DM patient population, it remains possible that SMBG can play an important role in the glycemic control with the appropriate supportive clinical education and follow-up of patients.

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"Voice and very forme becometh womanish": Contemporary medical views of the Castrati

Kate MacKeracher (Meds 2012)

Faculty reviewer: Dr. Paul Potter, Department of History of Medicine, UWO

During the 17th and 18th centuries, surgeons and parents attempted a bizarre endocrinological experiment: the castration of prepubescent boys for the preservation of their treble voices. The Baroque passion for highly ornamented, technically difficult, soprano-range music, combined with social restrictions to the training and performance of female singers, created unique opportunities for the castrati, or as they were more euphemistically called, the musici.1 Church choirs offered a reliable income and noble patrons promised prestige and influence.2 At the same time, Italian opera seria was becoming an internationally popular entertainment, opening up fantastic possibilities of wealth and renown for its castrati stars.3 Accordingly, ambitious families with slender means and abundant offspring chose to castrate younger sons with promising voices - openly through the 17th century, and with increasing shame and secrecy into the 19th century.4 From the perspective of modern endocrinology, the effects of removing both testes before puberty are significant. Without testes, a castrato would not pass through puberty, resulting in a prepubescent penis, sexual dysfunction, and sterility. More systemically, he would have no male-pattern body or facial hair and a "eunuchoid" body habitus (long limbs relative to torso, as the long bone epiphyses would not fuse). A lifetime of low testosterone would bring dry skin (arising from low sebaceous gland oil secretion), fine wrinkles, osteoporosis, a higher than average fat to muscle ratio, decreased libido, and possibly an increased risk of depression. The larynx would remain small, with short vocal chords, while the pharynx and lungs, dependent on growth hormone, rather than testosterone, for development, would reach adult proportions, resulting in a high frequency voice with adult power and resonance.5 Such is the lens 21st century medicine might use to view the castrati.

Yet this radical redesign of human male development occurred four centuries before the discovery of testosterone. What were contemporary medical perceptions of the castrati? What explanations did physicians offer for the effects of castration? In short, what did they see, and how did they make sense of it?

Technique

Although medicine at this time brought new attention to the study of anatomy, its practitioners still operated without reliable anaesthesia or sterile technique. Furthermore, castration was a somewhat clandestine medical procedure; it contravened Roman law in Italy, where the majority of castrati were made, and amputation of any part except when medically required was punishable with excommunica-

Effect

Although accounts of castration itself are scarce, medical writers often devoted space to describing its effects. Predictably, many noted an effect on voice; the British surgeon John Marten (d.1737) claimed castration was "[e]xperimentally known to change and advance the smallness and sweetness of the Voice."6 Other writers described the castrato voice in less flattering terms, for example, "squealing" in "Eunuchism Display'd," and "soft and shirle" in a mid-17th century translation of the "workes" of the French surgeon Ambroise Pare (1510-1590).7 Medical writers also noted a lack of beards among castrati, and there was general consensus about their infertility. The sexuality and sexual function of castrated men, however, was a much more controversial topic. For
example, one contemporary British physician implies castration removes both ability and desire for sex, while another claims quite the opposite:

Eunuchs love Women passionately, and being of a weaker Mind after than before Gelding, are the more susceptible of this Passion... It cannot be expres'd to what Point they will push their irregular Desires when their Fancy is once inflam'd...

This confusion mirrors castrati’s reputation in popular culture, which both mocked them as impotent and credited them with a myriad of lovers of both genders.

As implied in the above quotation, contemporary physicians considered castration to profoundly shape mind and behaviour, as well as body. A castrato, according to John Marten, has diminished “Strength, Activity, and Vigour of his body, and acuteness of his Reason and Judgement.”

The author of “Eunuchism Display’d” further claims that castrati have “no Courage or Bravery of Soul, but [are] ever timorous and fearful,” and contemporary medical authors tend to agree.

The Dutch physician Ysbrand van Diemenbroek (1609-1674) succinctly summarizes the general view by concluding that castration makes one “slower in all the Exercises both of Body and Mind.”

Different authors emphasise different attributes of castrati, but a general outline of 17th and 18th century medical descriptions would include a high voice, beardlessness, infertility, altered sexuality, physical and mental weakness, and cowardice.

Explanations

Medical rationales for this collection of castrati traits are complicated by the somewhat chaotic state of European medicine during the 17th and 18th centuries. The classical tradition, centred around the works of Galen of Pergamum (129-199 CE), had guided academic medicine through the Middle Ages, but new ideas from anatomy, alchemy, and various branches of natural philosophy were beginning to change medical writers’ understanding of the body.

The central problem was how castration could have such profound effects in apparently unrelated parts of the body. According to Galen, the testes help to convert blood into semen - the source of fertility and of sexual desire, in Galenic physiology - and aid the heart in producing the body’s strength and “innate heat.” Castrated men therefore are not only sterile, but also “chilled... and all their strength collapses.” Their cool, weak bodies are not able to produce a deep voice, beard, or body hair, which spring from heat and strength.

In Galenic physiology, gender difference arises from differences in bodies’ heat/cold, and to a lesser extent, dryness/moisture ratios: “The female is less perfect than the male for one, principal reason – because she is colder.” Castration removes a man’s heat advantage, bringing him down the spectrum of gender towards “imperfect” women: “the whole body is made feminine by excision of the testicles.” Yet the castrated man does not become a woman; he is “not female or male but some third kind.”

The ideas of loss of heat and a shift towards a feminine body inform the work of many 17th and 18th century medical authors. The British physician John Bulwer (1606-1656) directly cites Galen’s explanations, especially for the high voice of castrati. He also alludes to a “certain aire” – perhaps similar to Galen’s “strength” or “power” – given off by the testes, “by whose mediation virility is reconciled, the body acquires strength and firmenesse, is made more lively; at length, the principall members do more perfectly execute their office.” Loss of the testes is therefore a loss of “well-being.”

It also makes the castrato more like a woman, which is by no means a value-neutral transformation. Bulwer contends that to castrate a man for any reason except an “otherwise incurable disease” is unconscionable: “willingly to degenerate into the Nature of women, suffering themselves to be transformed from the Masculine to the Feminine appearance (a false Copy) is to offer as great an Injury to Nature as the malice of mans refractory wit can be guilty of.”

Ambrose Paré, too, cites Galen’s views on the subject, and elaborates upon the significance of degenerating “into a womanish nature”: “for they remaine without beards, their voice is weake, their courage failes them, and they turne cowards; and seeing they are unfit for all humane actions, their life cannot but be miserable.” Loss of heat brings not only female physical characteristics, but also moral (“they turne cowards”) and social (“unfit for all humane actions”) dimensions of 17th and 18th century femininity.

John Martin also relies on Galen’s ideas about the testes producing heat, but diverges from Galen and Bulwer about the effect of castration on sexuality. Since he considered semen to be the source of sexual desire, Galen held that castrated men would be essentially asexual. Martin explains his claims about the “irregular Desires” of the castrati by suggesting organs newly described by anatomists could be additional sources of semen: “the kind of aqueous Seed in the Prostata or seminal bladders irritates their Privities.” This “aqueous Seed,” combined with castrati’s “weaker” – that is, more female – mind, makes them more susceptible to desire. A belief that emasculation could undermine sexual restraint is in keeping with contemporary ideas about female sexuality in medical writing and in popular imagination. For example, Shakespeare’s King Lear describes his unfilial daughters as sexually voracious, despite an outward show of chastity:

Behold yond simpering dame... That minces virtue, and does shake the head To hear of pleasure’s name; The fitchew, nor the soiled horse, goes to ’t With a more riotous appetite. Down from the waist they are Centaurs, Though women all above. (IV, ii, 132-9)

Like the castrati, women have weak minds and ineffectual “seed” (ovaries were commonly – although not

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ineffectual "seed" (ovaries were commonly - although not universally - viewed as imperfect testes).\(^{18}\)

Diemerbroek is not content to use heat alone as his explanation for the consequences of castration. He employs more complicated reasoning partly drawn from the alchemy-inspired physiology of the radical medical theorist Paracelsus (1493-1541).\(^{15}\) According to Diemerbroek, the testes exude a "lustful seminal Breathing," which travels through the body, heating the blood and making the "Spirits" (active principles conveyed by nerves from the brain) more "smart and vigorous." Without this breathing, the blood grows cold, and the 'sulphury and oily Particles of the Blood' cannot be separated from the "more dry and salty Particles," resulting in more languid Spirits. Furthermore, the blood that would normally have been consumed in producing semen builds up, with the "effeminate" result of "extraordinary Corpulency" and a "more dull" mind.\(^{14}\)

The British physician Thomas Willis (1621-1675) combines Paracelsian alchemy with ideas about fermentation from contemporary natural philosophy to explain the castrati. The principles of salt, sulphur, and spirits are concentrated and fermented by the testes, as grapes are fermented to make wine; and from this "Semenal Ferment" arises "abundance of heat, great strength, a sounding Voice, and a manly eruption of Beard and Hair." As a result of castration, "men grow womanish," being cold, weak, high-voiced, and without a beard.

As an anatomist, de Graaf focuses on the anatomical basis for the way the testes affect the rest of the body. He suggests the newly-discovered lymph vessels "draw from the testicles, along with the thinner and more watery part of semen, other more noble parts and give a share of these to the heart and other parts of the body." Without these "nobler parts" of semen, a castrated male "changes in such a way as almost to acquire the physical condition of a female."\(^{16}\)

Although these explanations for the effects of castration diverge in the details, a few common elements emerge. They all postulate some mechanism for action at a distance - vital heat, seminal breathing, seminal ferment, noble parts of semen - in order to explain what the authors see as castration's dramatic changes to the body and mind. They also tend to portray these changes as a shift from a male state of being towards (but not to) a female one.

Significance

From this perspective, the prudent-seeming decision of a large, financially-strained family to have a musically-gifted son castrated becomes more radical. It would mean taking a child destined to be a "perfect" (that is, male) representative of what it means to be human - strong, bearded, rational, and brave - and debasing it to a more imperfect (female) creature. How much of academic medical writers' learned opinion would have been familiar to the parents and surgeons intimately involved in the operation is unclear. At the very least, Galen's views about the body had been circulating in Europe since the 12th century - and yet the

voice of a castrato was worth "cut[ting] out the strength of the entire body."\(^{16}\)

Quite apart from the philosophical implications, making a son more like a daughter had significant social and economic consequences. Castrati were technically forbidden to enter the priesthood (although exceptions were made), and professions outside music which did not admit women were not welcoming of "womanish" men.\(^1\) Since their transformation into women was incomplete, they could not claim a female social role, such as marriage or joining a convent.\(^1\) Consequentially, castrati had a profound incentive to succeed as singers; an application from a young castrato to a famous conservatorio in Naples makes this point clear: "since he is a eunuch, music... is the only profession to which he wishes to apply himself."\(^{1}\) This desperation, combined with the extremely rigorous early training it motivated, may have contributed as much as physiology to the voices contemporary audiences considered incomparable.

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6. See for example Giovanni Battista Morgagni's enormous work on pathological anatomy, De Sedibus et causis morborum per anatomem indagatis, first published in 1761.
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Diabetes and the built environment: Contributions from an emerging interdisciplinary research programme

Allanah Li (Meds 2012), Ashley Kim (Meds 2013), and Emma Farley (Meds 2013)
Faculty reviewer: Dr. Neil Arya, Director of Global Health, UWO

Introduction

Diabetes has become a global epidemic and rates continue to increase. Over 3 million Canadians have diabetes and approximately 90% of them have type 2 diabetes. Diabetes can lead to a reduced life expectancy and quality of life, and an increased risk of cardiovascular disease, kidney disease, blindness, and amputation. In addition to these personal health costs, diabetes may cost the Canadian healthcare system $16.9 billion per year by 2020.

The epidemic of type 2 diabetes is closely associated with a rise in obesity, poor diet quality, and physical inactivity. The failure of individual-level interventions such as medications and dietary counselling to forestall the epidemic has led to a strong interest in population-level approaches. There is growing recognition that aspects of the physical and social environment can have a powerful influence on health and health-related behaviours, at the individual, neighbourhood, and population levels. This article will explore the emerging interdisciplinary study of health with respect to the built environment and will discuss some of the important contributions of this field to understanding and addressing the diabetes epidemic.

What is the study of the built environment?

An interdisciplinary programme of study has emerged in the literature that examines the influence of the built environment on health outcomes. The built environment describes the physical layout of communities and encompasses land-use patterns, homes, schools, workplaces, stores, parks, roads, and transportation systems. Studies of the built environment acknowledge that aspects of our physical surroundings can shape choices about diet and physical activity – both important contributors to the development of diabetes.

Research in this field involves many diverse disciplines, including public health, epidemiology, nutrition, urban planning, geography, economics, sociology, anthropology, and leisure studies. Each of these disciplines has its own approach, expertise, and methodology when it comes to examining the relationship between health and the built environment. This article focuses particularly on the contributions of urban planning and geography. Study methodology generally falls into three categories: 1) interviews or questionnaires on residents’ perceptions of their environments; 2) systematic observations of area characteristics (i.e. number and type of restaurants in a given neighbourhood); and 3) analysis of existing data sets, often using Geographic Information System (GIS). GIS allows the integration, presentation, and analysis of data with spatial references, for example overlaying a database of supermarkets with a map of census boundaries. These disciplines and methodologies can reveal unique information about the diabetes epidemic and provide potential targets for intervention.

What can studies of the built environment tell us about patterns of diabetes?

One of the key associations between diabetes and the built environment is through food choices and diet. Studies have looked at how the food environment, which includes supermarkets, food stands, convenience stores, and restaurants, can differ by neighbourhood and how this relates to various health outcomes. One study of food store availability and neighbourhood racial composition found that none of the predominantly African-American census blocks examined in East Harlem had supermarkets or grocery stores. Another study found that fast-food restaurants were more likely to be found in lower income and higher traffic areas in King County, WA. Neighbourhood fast-food exposure has been associated with poorer diet quality and increased body mass index (BMI), particularly for local residents who do not own cars. According to a 2009 review article, residents with more access to supermarkets and limited access to convenience stores and fast-food generally have better diets and lower obesity rates. Moreover, those most affected by disparities in access to healthy food tend to live in low-income, minority, and rural neighbourhoods. These studies suggest that food choices and diet are influenced by multiple aspects of the built environment, including number and type of food stores, and that differences in neighbourhood access to healthy foods often reflect other demographic features (i.e. race, socioeconomic status).

The built environment has also been studied in relation to physical inactivity, another important contributor to obesity and the development of diabetes. Aspects of the built environment related to physical activity include access to recreation facilities, neighbourhood safety, open spaces, walking and cycling infrastructure, and length and nature of commute. Researchers in California established an association between obesity, physical inactivity, and commute time, as well as between obesity and vehicle miles of travel. One study found that greater neighbourhood physical activity resources were associated with lower insulin resistance, even after adjusting for age, sex, race/ethnicity, family history of diabetes, education, and income. The same study found that insulin resistance was also inversely related to neighbourhood healthy food resources, although this association was less robust. Furthermore, a longitudinal study found that better
neighbourhood resources, based on a composite score for healthy foods and physical activity, were associated with a 38% lower incidence of type 2 diabetes. Thus, certain features of contemporary North American urban design, such as a strong dependence on motorized transport and neighbourhood features that exclude opportunities to stay active, may be fuelling the diabetes epidemic.

A highly comprehensive study of diabetes and neighbourhood environments was conducted in Toronto and released in 2007. It received attention in the popular press, reflecting the nation's growing recognition for interdisciplinary solutions. The researchers examined 140 Toronto neighbourhoods, and assessed the relationship between diabetes and factors such as socioeconomic status, ethnic composition, crime rates, car ownership, public transportation, access to healthy food, opportunities for physical activity, and access to health care and other services. Neighbourhoods with high rates of diabetes tended to have a higher proportion of visible minorities, immigrants, and low socioeconomic status residents. Features of the built environment, however, played a significant role in mediating these effects. For example, poor, immigrant neighbourhoods had lower rates of diabetes than expected if they were found to be activity-friendly with good infrastructure, whereas more affluent neighbourhoods tended to have lower rates of diabetes regardless of whether they were activity-friendly or had good access to healthy foods.

Neighbourhoods with the highest rates of diabetes were in the more suburbanized northwest and east parts of the city, where there were not only high levels of poverty and visible minority residents, but also worse public transit, few opportunities for physical activity, poor access to healthy food, and low concentration of family physicians and diabetes education programmes. The complex relationship between diabetes, socioeconomic status, and neighbourhood resources was also shown in a Scottish study in the year 2007. Deprived areas were found to have lower than expected rates of type 2 diabetes when they were surrounded by less deprived areas with better resources.

What are the implications of built environment research on controlling the diabetes epidemic?

Urban sprawl has been linked to a variety of health-related concerns including air pollution, water quality, traffic accidents, and mental health issues. The studies described above indicate that urban design and aspects of the built environment can play an important role in the development of type 2 diabetes and its risk factors. Tackling the diabetes epidemic will require more than simply advising people to lose weight, eat better, and exercise more. There are features of our physical surroundings that can shape our individual and collective health and health-related decisions. These features include proximity of grocery stores, safe and pleasant opportunities for physical activity, and time spent commuting. The implications of this research are that changes can be made to the built environment to positively influence health outcomes. Neighbourhoods could be made more activity-friendly by improving sidewalks and bicycle paths, building recreation spaces, and instituting mixed land-use patterns in more suburban areas to provide better walking destinations. Diets may be improved by providing incentives for grocery stores to move into high-need areas, improving public transit so at-risk people can access healthy food, and developing policies that promote healthier choices at fast-food restaurants. The Ontario Professional Planners Institute has recognized the important relationship between community design and public health. However, making these kinds of changes would require collaboration between a diversity of stakeholders at all levels, including city planners, public health researchers, policymakers, community organizations, and grassroots initiatives.

Conclusion

The interdisciplinary study of health and the built environment is an important and growing field that can offer a unique contribution to chronic disease research. The built environment affects health at the individual, neighbourhood, and population level and can account for many of the spatial and demographic patterns in diabetes prevalence. Looking at diabetes rates from the perspective of the built environment can enhance our understanding of the emerging epidemic and can identify new targets for disease control and prevention.

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practice@mcmimed.com
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The sports doping race

Stephen Choy (Meds 2012) and Mayooren Ravichandiran (Meds 2013)
Faculty reviewer: Dr. Faisal Rehman, Department of Medicine, UWO

Introduction

Drug doping has a long history in sports. As the medical world introduced new pharmaceutical agents to restore muscle mass or improve blood oxygenation, the sports world in turn has sought to use these agents for similar gains. The progress in sports doping has catalyzed a parallel effort to detect doping abuse, with research labs exploiting new and improving old analytical technologies. The result is an endless race where each side tries to stay one step ahead. The next showdown will be at the 2010 Olympics in Vancouver, which will feature the most elaborate anti-doping program in the history of the Games. A new $8.9-million anti-doping lab will test about 2,400 urine and blood samples -- twice as many as the previous winter Olympics in Torino.1 While the lab will be testing traditional doping agents like testosterone, it is also equipped to deal with two doping agents that have recently plagued the sports world: analogues of erythropoietin (EPO) and human growth hormone (hGH). This article will outline the current methods to detect EPO and hGH doping, and discuss the future of the sports doping race.

Erythropoietin

Erythropoietin is a glycoprotein hormone primarily produced in the kidneys that stimulates red blood cell production. Recombinant human erythropoietin (rHuEPO) has been available since the 1990's for clinical use in patients with anemia; however, its therapeutic benefits have also extended to the sports world. rHuEPO can bolster an athlete’s red blood cell count and greatly improve his or her aerobic capacity.2 It has additional appeal as a doping agent because it is difficult to distinguish from naturally occurring EPO, and its therapeutic benefit lasts well after the original hormone clears from the body.

While rHuEPO was swiftly banned by the World Anti-Doping Association (WADA) in the 1990's, no method of detection was approved until a few months before the 2000 Sydney Olympics. A French anti-doping lab developed the method based on isoelectric focusing and a novel double immunoblotting technique.3 Some forms of rHuEPO have different patterns of glycosylation than endogenous EPO, resulting in different sets of isoelectric points (the pH at which a molecule has neutral charge). When placed in a gel with a pH gradient and an electric field, they will focus into bands where the pH is equivalent to their isoelectric point. These bands can later be marked by immunoblotting with monoclonal anti-Epo antibodies. The gel is blotted a second time under acidic conditions, which transfers only the anti-Epo antibodies to the second gel for subsequent visualization.

This direct method of detecting rHuEPO abuse has several shortfalls. For one, epoetin-omega and epoetin-delta, two available forms of rHuEPO, cannot be distinguished from endogenous EPO. Secondly, the detection window is roughly 7 days before circulating rHuEPO levels become too low.4 To overcome these limitations an alternative strategy has been proposed that looks at secondary blood markers of rHuEPO abuse.

The first attempts at detecting rHuEPO abuse in sports relied on simple tests such as measuring the hematocrit or hemoglobin. By 1993, sophisticated hematological analyzers came to market that allowed labs to make comprehensive measurements of secondary blood markers such as hemoglobin, percent reticulocytes, serum soluble transferrin receptors, EPO concentrations and percentage hypochromic red cells.5 The lack of sensitivity and specificity of these individual markers for detecting rHuEPO abuse led to the development of multiparametric models, which examine changes in groups of markers. Some models have been shown to detect EPO abuse after 14 days of washout.6

Indirect testing of rHuEPO abuse has not been favoured over direct testing. A positive result is not evidence that an athlete has taken the banned substance, since variability in blood marker profiles has been seen naturally and in athletes who train at high altitude. At the moment indirect testing has been relegated to serve as a screening tool for rHuEPO abuse.

Human growth hormone

Human growth hormone (hGH) is produced naturally by the pituitary gland to stimulate growth in the human body. Patients with hGH deficiency were originally treated using hGH obtained from cadavers, but now are treated with recombinant hGH (rhGH). Starting in the 1980s, athletes have been using rhGH to increase lean muscle mass, reduce fat content and increase strength. However, the International Olympic Committee (IOC) placed hGH on its list of forbidden substances in 1989. Similar to erythropoietin, rhGH abuse is difficult to detect because of its similarity in structure to hGH. Furthermore, detection tests cannot rely on hGH levels since hGH secretion is pulsatile and a plethora of factors, such as exercise, stress, hypoglycaemia and increased temperature, can naturally increase levels. Detecting rhGH abuse is considered the current greatest challenge to the anti-doping community.7

Recent research and advances in technology have allowed for some success in detecting hGH misuse as of the 2004 Olympic Games in Athens, Greece. Since hGH is a peptide with a very short half-life and less than 0.1% is excreted into urine, the most effective doping tests have been restricted to blood samples. Urine samples can be used...
to detect hGH using highly sensitive immunoassays. However, the problem of confounding factors causing variability in hGH levels can only be accounted for by performing out-of-competition tests to allow for comparison.

Blood tests have proven more effective and powerful and two methods are currently being evaluated. The first is a direct method for detecting rhGH in serum. This approach uses the fact that injected rhGH is exclusively a 22 kDa isoform, a pure molecular substance, while natively circulating hGH is present as a mixture of many forms. The test looks for an increase in the ratio of the 22 kDa isoform of hGH to the total hGH in the blood beyond a pre-determined threshold. For it to be effective, the test must be administered 24-36 hours after hGH injection. The second method tests for an increase in marker proteins influenced by hGH levels. These marker proteins have longer half-lives than hGH, making them much easier to detect.

A sure-fire method for detection and control of hGH doping remains elusive. The direct approach is the one currently accepted by WADA. However, promising research may yield a test using the marker-based approach in the near future. Genomic and proteomic profiling are currently being researched to discover new markers of rhGH abuse. One pilot study looked at the gene expression in leucocytes, which are altered directly by both GH and IGF-I. The hope is to characterize a gene fingerprint for rhGH abuse. Proteomic methods are being applied in a similar manner to create protein profiles using two dimensional electrophoresis and surface-enhanced laser desorption/ionization time of flight mass spectrometry (SELDI-TOF MS). A new frontier of sports doping is approaching with progress made in gene therapy technology. The idea is to introduce exogenous genes into an athlete's cells to produce virtually any protein or hormone in vivo. Current gene therapy trials are purely experimental and human use is still a long time away; however, the potential of this technology has already been demonstrated and has drawn much attention. Gene doping presents the ultimate doping detection challenge since the newly expressed protein is identical to the endogenous protein in terms of structure and mechanism of synthesis. To date, no definitive method of detection is available, although work is being done using DNA microarrays and gene expression profiling.

At the moment the doping community has an edge over anti-doping efforts despite the immense progress made over the last decade in detection technology. In some regards this result is a testament to the wide range of pharmaceutical products developed to combat disease. As the medical community tirelessly works to advance therapeutics, the doping race will still carry on.

References

Gender verification testing: Necessary for the integrity of international athletics, or inexcusable breach of personal privacy?

Colin Meyer Macaulay (Meds 2012), Moska Hamidi (Meds 2013),
and Karline Treurnicht-Naylor (Meds 2013)

Faculty reviewer: Dr. Cheril Clarson, Department of Medicine, UWO

On August 19, 2009, South African middle distance runner Caster Semenya set a world record in the women's 800m event at the world championships in Berlin. Closely following her stunning victory, the world athletics governing body, the International Association of Athletics Federation (IAAF) ordered her to undergo a process known as “gender verification testing.” A relative unknown just three weeks prior, Caster was unceremoniously thrust onto the world stage and has become a poster victim for a controversial practice that has been going on for decades.\(^6\)\(^7\)\(^8\) Subsequently, Australian newspapers announced that Caster had no ovaries or uterus, but did have undescended testes, and was in fact “intersex.”\(^2\)\(^3\) In order to explore the potential social and legal implications of such testing it is important to understand the history of so-called gender verification, as well as its medical advantages and pitfalls.

Science and medicine

The term “gender verification” is problematic because, as was detailed out in an open letter to South African journalist Mercedes Sayagues, gender is “the dominant society’s views on how women and men should look, behave, what roles they should play in society, how they should perform...”\(^4\)\(^5\) Sex refers to a biological dichotomy, whether one is male or female.\(^5\) Normal sexual differentiation is initially determined by chromosomal pattern, XX usually being female and XY usually being male. The presence of the SRY gene on the Y chromosome induces the undifferentiated gonad to commit to testis generation. The differentiated testis then secretes hormones that lead to the promotion of the male internal genitalia, and the regression of the primitive female internal genitalia. Subsequent conversion of testosterone to dihydrotestosterone (DHT) in the skin of the external genitalia leads to virilization of these structures and a complete male phenotype. The absence of the SRY gene leads to the regression of the male internal genitalia and a female phenotype.\(^6\) Of course, sexual differentiation is a complex process, and disorders of sexual differentiation (DSDs) may be chromosomal, gonadal or phenotypic (hormonal), leading one or more of these elements to be misaligned.\(^6\)\(^7\)

In 1968, in an effort to prevent male imposters from competing in the Olympics the IOC implemented mandatory “gender verification” of all female competitors.\(^6\)\(^7\)\(^8\) The test was a simple buccal smear that was then analyzed for the presence of sex chromatin (inactive X chromosomes or Barr bodies). The Barr-body test, though enticing in its simplicity raised significant concerns in the medical community. The test screened out XY females with no advantage over other females as is the case with complete androgen insensitivity (CAIS) or 46 XY/XX gonadal dysgenesis, while allowing those athletes with potentially advantageous conditions such as XX females with inadequately treated congenital adrenal hyperplasia (CAH) or XXY males to compete.\(^5\)\(^6\)\(^7\)\(^8\) Furthermore, the test was inappropriate in the first place since women with DSDs do not exhibit “characteristics relevant to sports performance...outside the range of possibility for XX females.”\(^6\)\(^7\)

History

Given what we now know to be true of DSDs, it may seem preposterous that the practice of sex verification was routine at the Olympics for more than 30 years. However, instances of subversion are not unheard of. In 1957 Herman Ratjen of Germany confessed he had been forced under the Nazi regime to compete as a female in the 1936 Berlin Olympics.\(^6\)\(^8\) Suspicion subsequently turned on hypermasculine female athletes from the Eastern Bloc following a number of female athletes undergoing gender reassignment surgery and subsequently living as men in the 1950s and 60s. Finally, in possibly the most high profile example, the 1932 women's 100m sprint gold medalist Stella Walsh was revealed to have chromosomal mosaicism and ambiguous genitalia during an autopsy following her death in 1980.\(^7\)\(^9\)

Initial attempts at gender verification in 1966 and '67 involved parading female athletes in front of a panel of medical experts in the nude, or even direct gynecological examination.\(^5\)\(^7\)\(^8\)\(^9\) This method of sex verification was fraught with ethical dilemmas and was ultimately abandoned in favor of the simpler and "less demeaning" buccal smear in 1968. The Barr-body test, originally conceived as a screening tool, became the definitive test of an athlete's femininity was used by the IAAF and IOC until 1992 when the IAAF abandoned the practice.\(^8\)\(^9\) Rather than follow the IAAF's example, the IOC switched from chromatin testing to analysis for Y chromosome material using PCR amplification, which it continued unabashedly until 2000. It is worth noting that since the advent of laboratory sex testing, no male imposter has ever been caught trying to infiltrate women's athletic events.\(^8\)\(^9\)\(^10\)

Social and legal implications of sex testing

Dr. Renee Richards, a nationally ranked men's tennis player, underwent a sex reassignment operation in 1975. In 1976 she attempted to enter the United States Tennis Open as a
Gender verification testing

woman. The United States Tennis Association (USTA) informed Dr. Richards that in order to enter, she had to pass a gender verification test; the first time such a test had been implemented by the USTA. Dr. Richards argued to the New York Superior Court successfully that the test was adopted for the sole purpose of preventing her from competing in the Open, and that moreover, the medical community regarded the test as "insufficient...and grossly unfair". Although this is the only case that rules on the issue of gender verification in sports as a matter of law, in 1985 Spanish national hurdler champion Maria Patino was disqualified from the World University Games and banned from international competition. Subsequently she went on to become the first woman to publicly protest this method of disqualification, and was eventually reinstated.

Given the IAAF and IOCs deplorable record of defending the rights of female athletes it should come as no surprise that as recently as 2006 an Indian woman, Santhi Soundarajan, was stripped of her silver medal at the Asian Games after failing a gender test. Ms. Soundarajan was later diagnosed with complete androgen insensitivity syndrome and was so psychologically traumatized by the experience that she has not competed since. Further confusing the matter is the fact that in the same year the IAAF released a policy on gender verification listing women with CAIS (among other conditions) as eligible to participate in international competition. In fact, the IAAF listed women with virtually all DSDs as eligible to compete, even those with conditions that theoretically might accord some physical advantages (i.e. CAH, androgen producing tumours, and PCOS). In light of this, the IAAF's policy statement then begs the question: What is the validity or necessity of gender verification in the first place, and why does the IAAF persist in using it?

Strict anti-doping rules guarantee that all winners and a random selection of other competitors provide urine samples under the supervision of officials. These rules likely provide enough disincentive for men to masquerade as women that such an issue is very unlikely to arise at all. Granted, the current guidelines for gender verification are substantially different than they were in 1968. They include stipulations that there be no compulsory standard gender verification, that determination of sex not be done solely on laboratory based testing, and a medical evaluation be performed by a gynecologist, endocrinologist, psychologist and an internist. What is unclear upon reading the IAAF's policy on gender verification are the circumstances under which a challenge of a competitor's gender may be legitimately raised. Article 12 of The United Nations Universal Declaration of Human Rights (UNUDHR) guarantees a person against "arbitrary interference with his privacy...and attacks upon his honor and reputation." Since the criteria for a legitimate challenge to a competitor's gender are not outlined in the IAAF's policy, it can be said that gender verification testing represents an arbitrary interference with an athletes' privacy. In 1996 the Norwegian parliament passed a law making genetic testing for the purposes of gender verification in sport illegal in Norway.

Furthermore, as argued by Pamela Fastiff, gender testing (as it was originally conceived and undertaken between 1968-1992 or 2000 in the case of the IOC) likely violates the fourth amendment of the American Constitution, as well as female athletes' rights to equal protection under the law. The fourth amendment guarantees "the right of the people to be secure in their persons...against unreasonable search and seizures". The ruling in the Renee Richards case upheld as a matter of law that the USTA could only use the gender test as a means to prevent fraud, and not to disqualify women with DSDs or transsexuals. Given this ruling and the arbitrary way in which gender verification testing continues to be applied, there are no valid circumstances under which a female athlete should have to fear disqualification on the grounds of failing a gender test.

Since no man has ever been caught masquerading as a female, it would appear that gender testing in any format is neither achieving its ostensible goal, nor serving athletes' best interests. Singling out young women with rare disorders and publicly humiliating them not only causes lasting psychological damage, but demonstrates the stunning insensitivity of the IAAF and IOC. From this analysis, it is clear that the only valid reason for conducting gender verification of any kind would be to ensure that young women like Caster receive the medical attention and psychological support they need, rather than to expose them to public scrutiny and scandal.

References


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UWOMJ | 79:1 | Spring 2010
Profile of Dr. Robert Hegele

Gordon Tsang (Meds 2012) and Joyce T. W. Cheung (Meds 2013)

Dr. Robert Hegele has been working in London, Ontario as a clinician-scientist with the University of Western Ontario (UWO) and the Robarts Research Institute since 1997. He obtained his medical degree from the University of Toronto in 1981, and went on to do a residency in Internal Medicine and sub-specialization in Endocrinology and Metabolism. He pursued further training in cardiovascular disease and genetics by doing fellowships at Rockefeller University in New York and the Howard Hughes Medical Institute in Salt Lake City, Utah. Dr. Hegele then returned to Canada, beginning his career at St. Michael's hospital in Toronto before finally settling in London, Ontario as a clinician-scientist at UWO. Dr. Hegele is the current Director of the Blackburn Cardiovascular Genetics Lab and runs a tertiary referral lipid clinic. Throughout his career, he has won numerous awards for his genetics research, and has made numerous discoveries.

Robert Hegele was born in Toronto to parents who emigrated from Russia. He recalls having a wide range of interests in his youth and demonstrated this by going on to pursue an undergraduate degree in music. Though Dr. Hegele did not have any early strong aspirations towards medicine, he cites his parents an influence in steering him and his brother towards pursuing medicine (his brother, Dr. Richard Hegele, is currently the Chair of the Department of Laboratory Medicine and Pathobiology at the University of Toronto). His mother was a medical student herself in Europe, but her studies were unfortunately interrupted due to World War II. Becoming a physician was also a logical choice for Dr. Hegele, providing him the opportunity to earn a comfortable living while giving him enough time for the pursuit of activities outside of his medical career.

We asked Dr. Hegele if there were any mentors that stood out during his time in medical school, and memorable experiences that he could recall.

"I still remember patients I saw in medical school, the first time I did a physical exam, a psychiatric evaluation of a depressed patient. What later propelled me were my personal relationships with patients, but also teachers and colleagues."

The presence of mentors guided Dr. Hegele’s interests in medical school, playing an important part in influencing him to choose endocrinology as a specialty. He also fell into a role of a researcher serendipitously. Initially desiring to teach, Dr. Hegele was told that in order to work at an academic centre, he had to also participate in research.

"People such as Dr. Hollenberg (1970-81) and Dr. Burrow (1981-88) were the Chairs of Medicine while I was in school. This tradition of endocrinologists as departmental chairs goes back to the discovery of insulin. So almost every chair of medicine in Toronto in the 20th century was an endocrinologist. Many of my mentors at Toronto General Hospital were endocrinologists, and they were the ones who encouraged me to pursue endocrinology."

We asked Dr. Hegele how he was able to endure through the many years of training to become an academic physician.

"It's a balance and reward [system], so we've all learned, but it's a different level [in doing research], your reward system is spread over a much longer time frame. Surgeons are the opposite, they need to be gratified almost moment to moment, and that's instantaneous. Somebody who is involved in research, you need to defer that gratification for years."

A typical week for Dr. Hegele involves teaching, research and seeing patients in his clinic. Approximately 80% of his time is spent in research and 20% in the clinic setting where he sees patients and teaches medical students and post-graduate trainees rotating through the lipid clinic. In the lab, Dr. Hegele and his team at the Blackburn Cardiovascular Genetics Lab work to understand the function of genes that are changed by disease. Where he differs from most physicians and researchers is that even though his position requires that he spend more time writing grants than filling in charts, he is never far away from his patients and truly has a unique perspective on their disease.

"Every research project started with a patient. Cardiology refers people with heart disease or severe cholesterol disorder or diabetes. We can now read the patient's whole genome profile using their spit or blood on a microarray. It allows me to try and find the molecular basis of their disease. Instead of indirectly deducing that a patient has inherited a gene from their family history, we can now know more definitively by screening their personal genetic profiles. We first started to look at two to three genes, now we're up to more than 30 genes for heart disease. Many genes that had no known function before recently, we try to learn what the gene product does, hoping to work backwards and eventually come up with a treatment.

"We see patients with lipid problems that are right off the scale. Often the usual drugs in the typical cardiology or community practice don't work [for these patients]. Studying their genetic profile to help come up with some new treatment, that would be [my goal]. Whether it's a drug or completely novel treatment plan, my goal in the next 5 years is to come up with something brand new for my patients with
severe dyslipidemia."

Many researchers are often poached by other universities, lured away by various reasons. Dr. Hegele is no stranger to recruitment, but has fortunately chosen to remain at UWO.

...One thing I like about London is that I have almost 2000 patients, and have established a personal relationship with each one. I wouldn't want to suddenly leave and not have the chance to say goodbye. I already did it once in Toronto, and it was difficult. The second thing is that I have a great balance and quality of life here. It's very manageable, the medical school and students are great, colleagues are great, my family is happy, I live close to work and I have a really nice house...we're really enjoying living in London." 

The recent economic downturn has affected the distribution of federal funding in many ways. We asked Dr. Hegele whether the recent downturn has affected his research.

"My time [spent in research] has increased. It's tougher to get research funding now, but I am a co-applicant on an NIH (National Health Institute) grant, part of the Obama stimulus package to NIH. I'm lucky to be a part of that. It's not quite the same in Canada. In general, I personally haven't felt it as badly, but research—like all aspects of the economy—has been hurting a little more."

We thought it would be interesting to get his thoughts on what he would like to see happen in the future, both in his career and in endocrinology.

"I'd really like trying to do something directly tangible (i.e. guidelines and clinical trials of new medications), so the bench research and experiments may diminish as I get older. I will focus more on translating the benefit to patients and health care providers on the front line. I liked the fact that endocrinology as a subspecialty was scientific...when I was training, a lot of clinician-scientists were endocrinologists. That has changed now to some extent. I also am committed to training. But there is an increased need for clinician-scientists in all fields in Canada. There need to be talented people who can speak both the language of medicine and of basic research. So I would want to see more MD/PhDs in the future and would try to foster that. I have three MD/PhDs working with me now— Piya Lahiry, Matt Lanktree and Chris Johansen. I want to make sure that there is a new generation of medical trainees who maintain an interest in science."

Outside his career in medicine, Dr. Hegele enjoys exercising and music. He also travels frequently to various conferences and meetings around the world, but still takes the time to enjoy his experiences. One memorable event he recounted for us was an opportunity to see a football match in Manchester, England earlier this year.

Before leaving his lab, Dr. Hegele showed us a piece of medical memorabilia that he inherited from Dr. James B. Collip, a former dean of Medicine at UWO (1947-1961) and the famous biochemist who worked with the Banting, Best and Macleod research team to purify insulin so that it could be used for testing in clinical trials. It was Dr. Collip's desk from his years at UWO.

This desk—where Dr. Collip worked—serves as a source of inspiration for Dr. Hegele in his scientific research, and a reminder of his ultimate goal of improving the quality of life for his patients.

Does he have some last words of advice for current medical students?

"Work hard, and play hard. Don't cut corners, but when you're relaxing, fully enjoy relaxing as well. You need to get exposure of a wide range of career options from the beginning... try to identify what you really like to do because that's what matters over the long term."

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Dr. Robert Hegele
(Seen in the background is a photograph of Dr. James B. Collip.)

Additional information
Read more about Drs. Gerard Burrow and Charles Hollenberg and the development of academic medicine at the University of Toronto at: http://www.deptmedicine.utoronto.ca/About_Us/History.htm

Read more about Dr. Hegele's research at the Robarts Research Institute website: http://www.robarts.ca/rob-hegele
Common side effects of diabetes medications

Kalpa Shah (Meds 2012)
Faculty reviewer: Dr. Terri Paul, Department of Medicine, UWO

In Canada an estimated 3 million individuals are affected by diabetes and the incidence of type 2 diabetes mellitus (T2DM) is expected to continue to rise. As the prevalence of T2DM rises, a larger portion of the population will be using diabetic medications, which underscores the importance of being familiar with the side effects of these therapies. The article will discuss some of the main classes of diabetic medications, their side effects and contraindications to use. The side effects of commonly used diabetic medications will be explored and discussed through a series of vignettes.

Case 1

An 82-year-old woman who lives alone is found by her daughter one morning confused, disoriented and sweating profusely. Her daughter is concerned that she is having a heart attack and calls the ambulance. The paramedics arrive and, on discovering the patient has diabetes, check her blood sugar. It is 2.0 mmol/L. She is given glucose and transported to the ER. As the physician treating her in the ER, you ask her the following:

- How long have you had DM? 2 years
- What medications are you taking? Metformin and glyburide
- Have you been eating appropriate meals? You find out that she has often just been having tea for breakfast but has been routinely taking her diabetes medications. She admits to often feeling “shaky” in the mid morning.

The patient is hypoglycemic which is confirmed by her low blood sugar. Although hypoglycemia is commonly associated with patients using insulin to control their diabetes, it is also a major adverse effect of insulin secretagogues - medications that stimulate the beta cells in the pancreas to produce insulin. There are two classes of insulin secretagogues: sulfonylureas and meglitinides. Sulfonylureas have been a mainstay of oral therapy for T2DM since the 1950s. They exert their effect by binding to the potassium channel in the pancreatic beta cells, which increases the resting potential of the cell. As a result, the cell is more sensitive to depolarization leading to a calcium influx and insulin secretion. Since sulfonylureas cause insulin release their major side effects are hypoglycemia, as seen in this case, and weight gain.

In this case, the patient was more prone to hypoglycemia since she was elderly and ate a very light breakfast when she took her medication. Other situations when hypoglycemia is more likely to occur include:

- after exercise or a missed meal
- when the drug dose is too high
- with the use of longer-acting drugs (such as glyburide)
- in patients who are undernourished or abuse alcohol
- in patients with impaired renal or cardiac function or gastrointestinal disease

Other side effects associated with the use of sulfonylureas include weight gain, rash (including photosensitivity) and nausea. Contraindications to the use of these drugs are sulfa allergy, pregnancy or lactation, type 1 diabetes mellitus (since there needs to be some functional beta cells in the pancreas for the drug to act on), cardiovascular disease, and impaired liver or renal function.

Case 2

A 65-year-old man has had diabetes for 8 years. He was initially treated with metformin and glyburide but as his control worsened, his glyburide was stopped and he was switched to insulin 30/70 taking 50 units BID along with his metformin. He comes to clinic complaining that he has gained 40 lbs over the past 3 months. His blood sugars before meals at breakfast are in the range of 5-8 mmol/L. He only occasionally checks at supper time but they are often 7-10 mmol/L. He says that he feels shaky and sweaty every morning at 10 am and must have a snack. He has been eating a sandwich and cookie as a mid morning snack. The same thing happens after supper, in the early evening when he feels that he must snack throughout the evening.

After asking him to check some blood sugars 2 hours after eating, you discover that he is having a low blood sugars of 2.5 mmol/L.

He is having symptomatic lows that he is over treating by snacking excessively and this is contributing to his weight gain. You could suggest switching to a shorter acting insulin analogue mixture such as Mix25 (humalog and NPH) or Novomix (novorapid and NPH) and adjusting dose. The ultra fast acting insulin will not last as long as the regular insulin 30/70 and he will no longer have the urge for a morning and evening snack. Another alternative is to transfer him to multiple daily injection (MDI), with fast acting insulin before meals and a long-acting insulin at bedtime.
Common side effects of diabetes medications

<table>
<thead>
<tr>
<th>Class</th>
<th>Prototype drugs</th>
<th>Action in the body</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylureas</td>
<td>Glyburide, glipizide, glimepiride</td>
<td>increases insulin secretion</td>
<td>Hypoglycemia, Weight gain, nausea, rash, GI symptoms, blurred vision</td>
</tr>
<tr>
<td>Meglitinides</td>
<td>repaglinide, nateglinide</td>
<td>increases insulin secretion</td>
<td>Hypoglycemia, upper respiratory infection, headache, diarrhea, weight gain</td>
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<tr>
<td>Biguanides</td>
<td>metformin</td>
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<td>GI symptoms, lactic acidosis</td>
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<tr>
<td>Thiazolidinediones</td>
<td>rosiglitazone, pioglitazone</td>
<td>enhances insulin sensitivity</td>
<td>Cardiac events, heart failure, edema, weight gain, fractures</td>
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<tr>
<td>alpha-glucosidase inhibitors</td>
<td>acarbose, miglitol</td>
<td>reduces absorption of glucose from gut</td>
<td>GI symptoms (diarrhea, flatulence cramping)</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>sitagliptin</td>
<td>inhibits breakdown of GLP-1 (a gut hormone that enhances insulin secretion)</td>
<td>upper respiratory infection, headache, sore throat</td>
</tr>
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Table 1. Summary of major classes of diabetic medications. Adapted from The Medical Letter.

He returns in 1 month after starting the new regimen and has lost 5 lbs.

Case 3

A 45-year-old woman presents with newly diagnosed diabetes and is started on metformin 500 mg TID. She returns 1 week later saying she cannot tolerate the medication due to upset stomach and diarrhea.

There are two classes of insulin sensitizers - medications that improve insulin action in the body: biguanides (which include metformin) and thiazolidinediones. Metformin is a first line oral hypoglycemic agent and some of the mechanisms through which it exerts its effects are: 1) decreasing hepatic glucose output 2) increasing insulin-mediated glucose utilization in muscle and liver 3) lowering serum free fatty acid concentrations thus reducing substrate availability for gluconeogenesis. It is believed that these effects are mediated through the activation of AMP-activated protein kinase. 5

The most common side effects of metformin are gastrointestinal (GI) and include a metallic taste in the mouth, diarrhea, abdominal discomfort, nausea and mild anorexia. These effects are reversible upon stopping the drug or reducing the dosage. 5 Metformin should be started slowly and with food to minimize side effect of GI upset as is illustrated in Case 3. Patients should be started with one pill or half a pill at mealtime once per day and this dose should be increased slowly as the patient tolerates it. The patient can titrate their dose themselves every 5-7 days up to a maximum of 4-5 tablets daily.

Another rare but serious side effect of metformin is lactic acidosis. As a result the following are contraindications to starting metformin therapy: impaired renal function, liver disease, alcohol abuse, heart failure, past history of lactic acidosis, decreased tissue perfusion or hemodynamic instability. 5

Case 4

A 50-year-old man with newly diagnosed type 2 diabetes mellitus has blood sugars in range of 8-12 mmol/L. He is started on Metformin and pioglitazone as initial therapy. He returns to your clinic in 3 months for follow up and his blood sugars are under much better control with fasting blood sugar of 5.7 mmol/L. However, he complains of a weight gain of 10-11 lbs (5 kg) and says his ankles and legs are puffy. You examine him and discover he has significant pedal edema that extends up his calves. He is not short of breath and has no signs of heart failure.

Pioglitazone has been associated with fluid retention, weight gain, heart failure, loss of bone mineral density and fractures.6-8 This patient is experiencing side effects of
Common side effects of diabetes medications

weight gain and edema from his pioglitazone therapy. His weight gain is due in part to fluid retention; the rest may be due to the proliferation of new adipocytes.

Pioglitazone belongs to the thiazolidinedione class of drugs. Thiazolidinediones are insulin sensitizers that increase the action of insulin by acting on adipose, muscle and liver to increase glucose utilization and reduce glucose production. It is believed that the thiazolidinediones exert their effect by binding to peroxisome proliferator-activated receptors (PPARs), which regulate gene expression. Fluid retention is caused by the binding of PPAR receptors in the nephron, which causes reabsorption of sodium and resultant fluid retention. This fluid retention often manifests as peripheral edema and may also precipitate heart failure in susceptible patients. PPAR receptors are also found in skeletal muscle, adipose tissue, pancreatic beta cells, liver, heart, and kidneys, which accounts for the varied effects of thiazolidinedione therapy.

References


Acknowledgements

We wish to thank Dr. Terri Paul, Division of Endocrinology and Metabolism, University of Western Ontario for providing the cases.
McCune-Albright syndrome: An unusual case of nasal obstruction

Anna Burianova (Meds 2012) and Julie Lebert (Meds 2013)
Faculty reviewer: Dr. Stan van Uum, Department of Medicine, UWO

Introduction

Nasal obstruction is one of the most common symptoms pediatric patients present to their physicians with. These symptoms are most often caused by allergic rhinitis and inflammation associated with viral upper respiratory tract infection, and thus it is easy to attribute all cases of nasal congestion to the more common entities in a busy clinical practice. The following case describes a patient with McCune-Albright syndrome (MAS), which presents as a rare cause of nasal obstruction. It is used to illustrate the need to maintain a high index of suspicion and a broad differential diagnosis, especially for cases not responding to initial treatment measures. Furthermore, it emphasizes the need to consider the presentation of the overall patient, and not just the presenting symptom.

Case report

An otherwise healthy 14-year-old girl presented with complaints of right-sided nasal obstruction. She failed to improve with a regimen of decongestants care as well as a course of antibiotics and mucolytics. Therefore, a computerized tomographic (CT) scan was ordered which revealed an enlarged inferior turbinate bone with significant right nasal obstruction, and a "ground glass" appearance of the inferior turbinate, middle turbinate, ethmoid sinus, sphenoid sinus, ossea and, as seen in this patient, nasal obstruction.1 ·6 FD was suspected. Further laboratory results showed normal growth hormone and prolactin levels. No distant sites of additional bone involvement were identified on bone scan, and all ophthalmologic tests were normal.

An endoscopic (submucosal) turbinoplasty was performed to relieve the nasal obstruction, and the subsequent histopathologic analysis of the biopsy displayed curvilinear trabeculae of woven bone surrounded by moderately cellular fibroblastic proliferation, again consistent with fibrous dysplasia. On follow-up evaluations, endoscopy revealed a stable inferior turbinate with no recurrence of the nasal obstruction. The post-operative follow-up CT scan demonstrated no change in size or shape of the lesion at 2 years following biopsy, and formal ophthalmologic examinations every 6 months have since revealed no change in vision.

Discussion

Epidemiology and clinical presentation

McCune-Albright Syndrome (MAS) has historically been identified based on the presentation of the typical triad of symptoms observed in this case: polyostotic fibrous dysplasia, café-au-lait pigmentation and precocious puberty.7 It is a rare disease which has been described in all races, with an estimated prevalence between 1/100,000 and 1/1,000,000.3 ·4 Females are more often affected than males with a ratio of 2-6:1, and are also more often observed to have sexual precocity.4 ·5 However, because autonomous hyperfunction of nearly every endocrine organ has been associated with MAS, a more clinically relevant definition which is broader than the original triad has been proposed.3 ·4 More extensive manifestations of MAS have also been reported, including hepatobiliary disease, cardiac arrhythmias and CHF, pulmonary dysfunctions, proximal renal tubules malfunction, and sudden or premature death.1 ·4 ·5

Fibrous dysplasia (FD) is a benign tumour of fibrous tissue, where the normal components of bone fail to differentiate into mature structures. The growth of chondrocytes and immature spindle fibroblast-like cells results in calcification and a ground-glass appearance, with the histological hallmark being an extensive proliferation of fibrous tissue within the bone marrow.6 The most common site of involvement is craniofacial and may result in exophthalmos, tooth development abnormalities, visual disturbances, facial asymmetry, hearing abnormalities, leontiasis ossea and, as seen in this patient, nasal obstruction.1 ·6 FD can also be found in the proximal femur, pelvis and vertebral column and typically affects medullary rather than cortical bone.1 Under-mineralization makes the bones prone to fractures and deformities, and patients often present with bone pain.1 Although malignant transformation is rare (0.4%), it is more common in MAS patients (4%).1

Café-au-lait spots are pigmented cutaneous markings, which are present at birth or develop shortly thereafter.7 They are distinguished by the jagged "coast of Maine" shape of their borders, and typically found on the nape of the neck or crease of the buttocks.7 Their distribution tends to follow the lines of Blaschko, with a tendency to stop at the midline on the same side as the predominant bone lesion.4 ·7

Precocious puberty in girls is defined as the development of secondary sexual characteristics before the age of 8 years. Although the exact onset of puberty in this patient was unknown, it usually affects females with MAS between the ages of 1 and 6 years and is gonadotropin-releasing hormone-independent.8
McCune-Albright syndrome

Many other endocrinopathies are often associated with this syndrome: pituitary gland abnormalities include growth hormone and prolactin hypersecretion; adrenal gland disorders include hypercortisolism, acromegaly, and Cushing’s syndrome; thyroid gland disorders include hyperthyroidism, nodular goiter, and follicular adenoma; and parathyroid gland abnormalities can include parathyroid adenoma, and hyperparathyroidism.1

Genetics and molecular basis

The sporadic occurrence of MAS, its variable presentation and the pattern of skin pigmentation initially led to the hypothesis that this disorder is secondary to an autosomal dominant mutation occurring early in embryogenesis.5 Molecular studies have since identified a missense mutation in the GNAS1 gene, which codes for the alpha subunit of a guanine nucleotide-binding regulatory protein, Gαs.1,3 Gαs is involved in the stimulation of adenylyl cyclase; mutations associated with this syndrome are gain of function mutations.9 The constitutional activation of Gαs leads to increased levels of intracellular signaling molecule cAMP, which in turn lead to increased production of a variety of different molecules. The up-regulated molecules can include melanin, estradiol, testosterone, thyroxine, growth hormone and cortisol (Fig 1).3 Generally such mutations are not compatible with life; however, it is thought that these patients survive as mosaics because the change in the GNAS1 gene occurs during the early embryonic postzygotic stage.3 This mosaicism is seen in part as the pattern of café-au-lait spots, and is further supported by the wide spectrum of clinical presentations observed in patients.3 The phenotype and severity is determined by the cell line involved in the mutation, while the severity relates to the point in development that the mutation occurred.3

Diagnosis and treatment

The diagnosis of MAS is usually made based on clinical findings. The evaluation of patients should therefore be guided by knowledge of the spectrum of tissues that may be involved, with specific testing for each. Although genetic testing is not routinely available, genetic counseling should be offered with the assurance that there is no vertical transmission of the disease.3 Because there is no specific treatment to correct for the mutation of Gαs, treatment needs to focus on controlling the spectrum of symptoms that may arise from this syndrome. For females, testolactone has been the mainstay of treatment as it decreases serum estradiol and estrone levels by competitive inhibition of aromatase.1 Ketoconazole and spironolactone possess anti-androgenic activity and are effective in males.1 PTU, methimazole and radioactive iodine are useful in hyperthyroid states, and octreotide suppresses GH secretion and slows acromegalic growth.1 Surgical therapy can be used to remove the source of hormone hypersecretion, and is useful in cases refractory to medical therapy.1 Surgical resection is the only cure for fibrous dysplasia, but may be technically difficult in the skull and facial regions. In these cases, the risk of complete resection must be carefully weighed against the potential benefits.1 There is no proven medical therapy, though bisphosphonates have been used to reduce the incidence of fractures and reduce bony pain. Calcium, vitamin D and phosphorus supplements may also be used.3

Figure 1. Molecular mechanism of McCune-Albright syndrome.1
McCune-Albright syndrome

References


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Small bowel intussusception from metastatic melanoma

Brett Howe (Med 2010)
Faculty reviewers: Drs. Robert Humphrey and William J. Wall, Department of Surgery, UWO

Case report

A 46-year-old female presented to hospital with sudden onset lower abdominal pain, associated with nausea, and decreased flatus and bowel movements over a 24 hour period. Frequent bilious vomiting developed shortly thereafter and her pain worsened. Ten years ago she had excision of a melanoma of the scalp combined with a modified radical neck dissection. No evidence of recurrence had been noted.

Physical exam revealed a mobile, firm, tender mass in the lower abdomen. Abdominal ultrasound identified fluid filled loops of small bowel, suggesting an obstruction. Abdominal series was non-specific but a CT scan suggested a closed loop obstruction in the mid-ileum without evidence of ischemia (Figure 1).

At laparotomy, an ileal-ileal intussusception was identified, resulting in a segment of ischemic ileum and a high grade small bowel obstruction. No effort was made to reduce this segment as the suspected pathology was metastatic melanoma based on the history. A 90.0cm segment of small bowel was resected and a primary anastomosis was performed. The remainder of the laparotomy revealed no evidence of metastatic disease. The specimen was opened in the operating room revealing a 2 cm pedunculated darkly pigmented polyp as the lead point. Final pathology was consistent with metastatic melanoma to the mucosa and submucosa of the small bowel. The patient had an uneventful recovery, but less than a year later developed metastatic melanoma to her lungs.

Discussion

Melanoma is a malignant tumour arising from melanocytes that are found in the integument as well as the inner ear, GI tract mucosa, and eyes (conjunctiva). It is the most deadly form of skin cancer. In 2008 it was estimated to be the 7th most common cancer diagnosis in Canada with an estimated 4600 Canadians diagnosed with the disease and 980 deaths. Metastatic disease from a cutaneous melanoma is most commonly detected clinically in skin, subcutaneous tissue and nodes, lung, liver, and brain. Although symptomatic GI tract metastases occur in only 1-7% of individuals with metastatic melanoma, autopsy studies report occult metastasis in up to 60% of cases.

Melanoma is the most common metastatic tumour affecting the GI tract. All histological subtypes are capable of metastasising to it, though superficial spreading melanoma is the most common subtype found. The small bowel is most frequently involved (58-71%), followed by the stomach (27%), colon (22%), and esophagus (5%). Common presenting symptoms are abdominal pain, bleeding (gross or occult), mass, or obstruction, with the latter being most commonly a result of intussusception. The timeframe from occurrence of a primary lesion to
Small bowel intussusception from metastatic melanoma

Symptomatic metastatic disease is exceptionally variable. Previous studies have shown median disease free survivals between 25.3 months and 24 years. Median survival after GI metastases is estimated to be 12.5 months, with a 5 year survival of only 14%. Surveillance for metastatic disease in individuals with a primary melanoma is controversial. The role of positron emission tomography (PET) scanning is evolving. It offers sensitivities of 79 to 100%, but is limited by accessibility and cost. CT scans have only 60-70% sensitivity for detecting small bowel melanoma, however they are often the first line of imaging due to their accessibility.

A previous study of CT scanning for staging of primary melanomas found positive results in 29 of 151 patients. However, biopsies and follow-up studies found only 2 patients with metastatic disease. Currently, there are no recommendations for intense follow-up in patients with primary melanoma beyond 5-10 years except for lifelong dermatologic surveillance due to the prevalence of second primary melanomas.

Treatment of GI metastasis largely depends on how advanced the disease has become and the overall physical condition of the patient. Therapeutic or palliative surgical resection is almost always indicated for local lesions that have become symptomatic. This is especially true for patients with acute abdominal pain and signs of obstruction. Numerous studies have demonstrated improvement in symptoms and survival with GI resection and a low morbidity and mortality rate associated with the procedure. The role of adjuvant therapy (chemotherapy, immunotherapy) after resection of metastatic GI melanoma is unclear.

References

Yams for breakfast, lunch, and libido? A critical look at bioidentical hormone therapy

Justin Chia (Meds 2012)
Faculty reviewer: Dr. Ruth McManus, Department of Medicine, UWO

Background

It has only been in the recent past that the Women's Health Initiative (WHI) changed how physicians and consumers viewed postmenopausal hormone therapy (HT). The estrogen-progestin arm of the study, involving over 16,000 women, was stopped prematurely due to findings suggesting an associated increased risk of stroke, breast cancer, and dementia without a reduction in cardiovascular risk.1

Subsequently, women have been searching for "safer" alternatives to treating their climacteric (menopausal) symptoms — including hot flashes, decreased libido, vasomotor changes, urogenital atrophy, skin changes, increased body weight and abdominal fat, and psychophysiologic changes like mood changes, insomnia, and anxiety.2 One alternative that has been offered to women is "bioidentical hormone" therapy (BHT), which is purported to be safer, natural, and more efficacious compared to standard post-menopausal HRT.

Defining bioidentical hormone therapy

BHT is a term used to describe plant-derived precursor compounds (eg. diosgenin from Mexican yam, stigmasterol from soy), which have been synthesized in the laboratory to be structurally identical to endogenous human hormones such as estrogen (estrone, estradiol, estriol), progesterone, testosterone and dehydroepiandrosterone (DHEA).2 Perhaps a more accurate name for bioidentical hormones should be native synthetic hormones, as these hormones are not found naturally in any plants.3 Proponents of BHT claim that it is capable of restoring a balance between hormone levels, and yet due to similarity to human hormones along with individualized dosing, it is able to provide symptom relief with minimal side effects.5

Those who favour BHT affirm that the first step in determining the usefulness of BHT is a salivary hormone profile, looking for deficiencies in sex hormones. Steroids easily diffuse into the saliva and in some cases may accurately reflect free hormone levels. For instance, midnight salivary cortisol is an evidence-based, validated test for Cushing's syndrome. However, BHT proponents expand their diagnostic range and offer an entire panel of various hormone testing through mail-order kits. Interested consumers can mail in a saliva sample (collected by chewing on a cotton ball, placed in a plastic receptacle) and then they will receive an extensive computer print-out with their results as well as an explanation of findings and possible correlated symptoms.5 The inexpensive nature of the test and the relative ease of obtaining samples make this test particularly popular with consumers and BHT advocates.

Once the salivary results are obtained, the BHT practitioner will prescribe a course of bioidentical hormones, and tailor the dosage specifically to the individual's hormone profile. In some cases, special preparations can be created by pharmacists. BHT comes in creams, gels, pills, patches, self-injectors and pellet therapy. Within the various treatments are hormones such as estrogen, progesterone, cortisol and "women testosterone."6

According to one company's website, the cost of BHT can exceed $5000USD per year. An initial consult is $400, follow-up consults $185 (of which you need three), and the cost of treatment may range from $75-350 per month. Further costs come with the treatment itself and laboratory tests.7 Because insurance companies do not cover the cost of these treatments, this may be a limiting factor for many patients. Keeping this in context, daily Premarin 0.625 mg along with Provera 2.5 mg would be around $700USD per year, even with the 800% increase in price in 2009.8,9

Currently, there are numerous commercial as well as individually prepared "natural" products. Formulations are created by pharmacies according to prescriptions written by referring practitioners, and cannot all be purchased commercially. One such product is Biest (bioestrogen) which is a combination estrogen containing 20% E2 (estradiol) and 80% E3 (estriol), expressed in a milligram per milligram basis.10 Another such formulation used frequently is Triest (triestrogen) which contains 10% E2, 10% E1, and 80% E3. It is important to note the relative potencies of the estrogens: E1 (estrone) is the most potent, followed by E2, and E3 is the weakest of the three, being the final end product of E2 and E3 metabolism. The presence of such a high proportion of E3 in these mixtures is advertised as the key to reducing adverse side HRT effects while still conferring symptom relief.19

What is the evidence from medical literature?

There have been few evidence-based trials looking at the safety, efficacy, and durability of BHT. According to proponents, because the steroids are found in nature, are not extensively manufactured, and are dosed in a way that is individualized, there is no need to research these compounds and therefore submit data to FDA for approval and regulation.5 In addition, pharmacies can mix their products differently, which makes it difficult to standardize and determine the risks associated with BHT.

Despite salivary hormone testing (SHT) developing a medical literature showing usefulness in certain areas of clinical practice, it is often criticized for its lack of reliability and inability to correlate symptoms and hormone levels. Standard HRT prescribes estrogen and progestins in doses...
that provide symptom relief. In the BHT approach, SHT test results may persuade asymptomatic women to take doses they may not need and symptomatic women to take excessive doses.11

In theory, saliva is similar to ultrafiltrate and should correlate with free/unbound serum concentrations. However, it has been shown that these correlations vary depending on the time of day, diet and the specific hormone tested.12 Many hormone levels vary during the day, week, month, season and therefore a one-time SHT may be inadequate for diagnosis or monitoring dose adjustments, particularly unless greater than 5 samples are taken daily.2

Traditional medicine uses individualized dosing for drugs which have a narrow therapeutic index, as described by population-based pharmacokinetic studies (eg. cyclosporine, digoxin). According to Jelliffe, true individualized dosing must be predicated upon a known target serum concentration, at a desired target time after the dose, for each patient.13 However, proponents of BHT have no studies dealing with important pharmacokinetics of their drugs such as volume of distribution, protein binding, route of elimination, among other factors.14 Without a predictable relationship between dose and response of the drug, it becomes impossible to know how much medication to prescribe.

As mentioned previously, the BHT hormones typically used for menopausal symptoms are estrogen and progesterone. But how much estrogen is really in these compounds? In addition to inter-pharmacy differences of product formulation, there appears to be another underlying problem—ratios may not be what they seem. Biest, an 80:20 ratio of E3 to E2, is not based on the estrogen potency of each compound, but rather is based on the milligram quantity of different agents added together. For example, if a woman takes 2.5 mg of Biest (2.0 mg E3, 0.5 mg E2), and the potency of E2 is 1/80th of E3, the equivalent content of E2 is actually 0.525 mg.15 Some women may take 2.5 mg Biest twice daily, increasing the E2 equivalent to 1.05 mg per day which is a dosage exceeding most prescribed estrogen therapies. The same applies for Triest, which is a combination of estradiol, estradiol, and estrone.2

With E1 being the least potent of the estrogens, its high percentage in BHT formulations is believed to decrease the incidence of breast cancer and endometrial hyperplasia. However, past studies have shown equal endometrial stimulation from estradiol and estradiol medications.13 Estriol was also found to partially overcome antiestrogen inhibition from Tamoxifen, even when Tamoxifen is present in 1000-fold excess. Therefore, estriol does not have a protective role in human breast cancer, and all estrogens bind to an equal number of sites when saturating concentrations are used.14 It can be deduced that despite being the least potent estrogen, E1 still carries risks of cancer that BHT tries to avoid.

Much has been written about progesterone in BHT. Although that extensive literature will not be reviewed here, it should be noted that many of the health claims from BHT practitioners have not been substantiated, but rather have been overshadowed by evidence-based medicine. For example, BHT practitioners claim progesterone increases metabolism and causes weight loss. However, no studies are identified to support those claims. Indeed, weight gain, rather than loss, has been shown with progestin therapy in cancer-related anorexia.15

Practice guidelines for the physician

In view of the evidence, how should the physician respond to BHT practitioners and claims? The North American Menopause Society, the American Association of Clinical Endocrinologists, and the Endocrine Society have all published positional statements expressing concern for the safety of women using these products.16–18 These groups are currently advocating for FDA oversight in the standardization of drug purity, the need for mandatory reporting of adverse events, as well as uniform labeling of precautions on BHT formulations.

The bottom line from these groups involves strong recommendations that BHT not be used in the treatment of menopausal symptoms. It is argued that both "bioidentical" and "traditional" hormone replacement treatments will carry essentially the same risks and benefits if dosage and

<table>
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Table 1. A comparison of traditional and bioidentical hormone therapy.

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41
purity are equal. Therefore, no matter the source or hormone regimen, the "individualized" dosing must be carefully controlled.

A summary of the Endocrine Society's comparison of BHT and HT is shown in Table 1. Overall, further research and an evidence-based scientific approach must be applied to BHT to validate or debunk its proposed health benefits. Until then, it might be best to keep the yams on the Thanksgiving table instead of using them to treat human conditions.

References

Why did Harvey Cushing misdiagnose Cushing's disease? The enigma of endocrinological diagnoses

Laura Hinz (Meds 2011)
Faculty reviewer: Dr. Ruth McManus, Department of Medicine, UWO

The case of Minnie G

Minnie G's menses started at the age of 14 and were regular for two years and then suddenly ceased. She began to grow stout and in two years her weight had increased from 112 to 137 pounds. She suffered a great deal from headaches, nausea and vomiting. She complained also of aching pains in the eyes which latterly had become prominent, and there had been occasional periods of seeing double. Other noteworthy symptoms were insomnia, tinnitus, extreme dryness of the skin, frequent sore throats, shortness of breath, palpitation, purpuric outbreaks, recurring nosebleeds, and marked constipation. A definite growth of hair had appeared on the face with thinning of hair on the scalp. She had become increasingly round-shouldered. Muscular weakness had become extreme and there was constant complain of backache and epigastric pains.

Case discussion

This case represents the original words of Harvey Cushing in describing Case XLV, a woman who came to be known in the literature as Minnie G or MG. The description appeared in Cushing's seminal work, *The Basophil Adenomas of the Pituitary Body and their Clinical Manifestations* in 1932. Cushing first saw MG in 1910 and originally attributed the complaints of obesity, diabetes, hirsutism, and adrenal hyperplasia to myxedema. He then changed his differential to "pituitary, adrenal, or ovary?" Over the next 20 years, Cushing saw MG twice more and began an extensive review of the literature. His previous work on acromegaly led him to postulate that if acidophilia could lead to growth hormone excess, then perhaps basophilia could lead to cortisol excess. An 1990 case description by Cushing's mentor, Sir William Osler, helped Cushing to finally determine in 1932 that MG's symptoms were the result of a cortisol secreting pituitary adenoma.

The case of Minnie G illustrates a common diagnostic challenge in endocrinology: endocrine conditions often are associated with a non-specific symptom set, which combined with individual variability can have the result that some patients go undiagnosed or are misdiagnosed. If even Harvey Cushing struggled with the diagnosis of Cushing's disease, what hope is there for humble endocrinologists and general practitioners? This article will use Cushing's disease as a prototype to explore how and why symptoms are grouped into diagnoses, and the associated perils and advantages of this practice.

The diagnostic approach to Cushing's Disease

Cushing's disease is one form of Cushing's syndrome, a group of symptoms that result from hypercortisolism. Diagnosis of Cushing's disease depends on clinical, laboratory, and imaging modalities. For instance, a diagnosis of Cushing's disease requires evidence of hypercortisolism; the excess cortisol must be the result of high ACTH levels; and the high ACTH must be the product of a pituitary adenoma.

The following algorithm aims to fulfill those three criteria:

1. Does the patient exhibit symptoms of cortisol excess?

<table>
<thead>
<tr>
<th>Test</th>
<th>Results suggestive of Cushing's syndrome</th>
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<tbody>
<tr>
<td>Observation</td>
<td>Truncal obesity</td>
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<td>Facial plethora</td>
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<tr>
<td>Laboratory testing</td>
<td>Glucose intolerance</td>
</tr>
</tbody>
</table>

2. Is there actually cortisol excess?

<table>
<thead>
<tr>
<th>Test</th>
<th>Results suggestive of Cushing's syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>11pm salivary cortisol</td>
<td>&gt;4x increase</td>
</tr>
<tr>
<td>Serum cortisol after low dose dexamethasone suppression test</td>
<td>&gt;54nmol/L</td>
</tr>
<tr>
<td>24 hour urine free cortisol</td>
<td>&gt;250nmol/day</td>
</tr>
</tbody>
</table>
The enigma of endocrinological diagnoses

3. Is the cortisol excess ACTH-dependent?

<table>
<thead>
<tr>
<th>Test</th>
<th>Results suggestive of Cushing's syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum ACTH</td>
<td>&gt;40 pmol/L</td>
</tr>
</tbody>
</table>

4. Is the excess ACTH from the pituitary?

<table>
<thead>
<tr>
<th>Test</th>
<th>Results suggestive of Cushing's disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI</td>
<td>Pituitary adenoma</td>
</tr>
<tr>
<td>Petrosal venous sampling</td>
<td>High ACTH levels in the region of the pituitary</td>
</tr>
</tbody>
</table>

The enigma

Algorithms such as these suggest that diagnosis of disease should be relatively straight-forward. However, the fact that Cushing took 20 years to diagnose the disease that bears his name combined with the fact that most patients wait 6 months-10 years between symptom onset and diagnosis of Cushing's disease suggests otherwise.² Cushing's disease is simply an example of a broader issue: how and why do we group symptoms into categories, and what problems do these groupings create?

How do we define disease?

A disease is a collection of recognizable symptoms that result from a common cause. This definition is slightly narrow, as diseases are defined not only by their symptomatology and pathology, but also by imaging and laboratory results, response to treatment, and epidemiology. At first glance, the definition of a disease should be fairly simple. Even the layperson can recognize that diabetes is not the same as influenza. The problem arises when symptom and investigation differences are more subtle: even the most experienced endocrinologist will struggle with differentiating a pituitary basophilic microadenoma from ectopic ACTH production. This struggle is analogous to the definition of a species—biologists recognize that a cat is not a dog, but grouping like micro-organisms is a different challenge.

From this analogy, we recognize that defining an entity is much more difficult when we are unable to see it clearly. The distinction between a cat and a dog is simple because we can compare ear shape, bone structure, sounds produced, and habits. Grouping micro-organisms requires microscopic examination and molecular techniques. Endocrinology is the micro-organism of the medical world: it deals with conditions that are often visible only in their clinical manifestations, not in their causative agents.

Cushing's disease is somewhat unique in that an anatomical anomaly, a brain tumour, is the etiologic mechanism. In contrast, hypercortisolism is recognized only by the clinical manifestations of hypertension, obesity, and glucose intolerance and by laboratory abnormalities.

In defining disease, establishing criteria for a syndrome is perhaps the most difficult task. Syndromes are collections of symptoms, signs, and investigational results that have a similar course and response to treatment. However, syndromes are made up of sufficient rather than necessary elements. That is, the symptoms make the diagnosis more likely, but there is no one symptom that will absolutely rule in or out the diagnosis. Endocrinology is fraught with vague symptoms, largely because the definition of normal is elusive. Hormone levels fluctuate throughout the day, with age, with environment, with diet, and between individuals. It is incredibly difficult to define 'normal' for a measurement that is not only inconsistent between but also within individuals.

Why do we define disease?

Because the symptoms that make up a syndrome are so variable, it is perhaps appropriate that they are named after the people who first described them. Diseases are, in essence, a human creation. They are an attempt to impose order and allow parsimonious treatment. Cushing argued that defining disease was important because "a peculiar clinical syndrome has first been described by someone with a clarity sufficient to make it easily recognizable to others." It is only by having an accurate definition that different physicians are able to make the same diagnosis.

If a collection of symptoms has a common cause, it is easier to treat the cause than it is to treat each individual symptom. Consider the example of Cushing's disease:

![Pathogenesis of Cushing's disease and diagnostic tests](image)

Note that the diagnostic tests described above detect...
The enigma of endocrinological diagnoses

Cushing's disease is the recognition of clinical symptoms. However, when viewed in isolation, these symptoms can be characteristic of numerous diseases. Many patients who are ultimately diagnosed with Cushing's disease find themselves passed between specialties before an astute physician finally integrates the symptoms into a whole. For instance, Evans et al describe a woman who saw a dermatologist, cardiologist, orthopaedic surgeon, and psychiatrist before ultimately diagnosing herself from information in the lay press. This illustrates a fundamental flaw with the current medical system- subspecialisation ensures expert care of specific symptoms, but it may neglect to view the patient as a complete person. Diagnostic re-evaluation is needed as time and symptoms evolve and an astute physician looking at the entire person may be seminal in putting the pieces together. Optimal communication is required between specialists to ensure that a common cause of symptoms can be found if it exists.

As seen in Figure 1, the first step in the diagnosis of Cushing's disease is fraught with perils at multiple levels:

- **The Disease**
  - Atypical presentation
  - Intermittent hypercortisolism
  - Pituitary incidentalomas
  - Adrenal incidentalomas
  - Rare forms
  - Macronodular adrenal hyperplasia
  - Abnormal sensitivity to glucocorticoids
  - Pheochromocytoma
  - Pseudo Cushing's
  - Obesity
  - Anorexia
  - Alcohol
  - Depression
  - Stress

- **The Patient**
  - Symptoms are interpreted in light of education, culture, relationships, etc.
  - Comorbidities
  - Subpopulations present differently: pregnant women, children
  - Lifestyle effects (diet, exercise, exogenous hormones)

- **The Tests**
  - The definition of 'normal' is not absolute
  - Timing: Symptoms require longterm glucocorticoid excess, and levels of cortisol vary throughout the day
  - Imperfect lab tests, none are 100% sensitive or specific
  - Tests require patient compliance (ex. 24 hour urine collection)

- **The Physician**
  - Rare disease, may not consider it

- **The Medical System**
  - Imperfect communication between specialists
  - Ignoring parsimony: diagnosing the symptoms instead of the syndrome
  - Specialty-specific care

Figure 2. Complicating factors in the diagnosis of Cushing's disease.

Conclusions

The diagnosis of Cushing's disease can be enigmatic and elusive, but, as evidenced by the following letter from Minnie G to Cushing, ultimately rewarding:

"Dear Sir: Of course, I am very sorry to trouble you again with letters, but I am taking advantage of your own words. The great pains my body is forced to bear can be honestly compared to the modern German artillery.... And now I have told you most all. I do believe sufficient amount and I ask you again, what can you do? There must be some palliation in my letters for I regard you as my best friend and doctor. Yours sincerely, Minnie G."

Cushing may have originally misdiagnosed the disease that bears his name, but he was a brilliant physician who was a friend to his patients. His devotion was such that he actually resided in the hospital to better care for his patients.

The case of Minnie G thus highlights a number of the vital components of endocrinological diagnosis:

- A high index of suspicion.
- Careful vigilance and reassessment of diagnostic assumptions.
- Communication between specialists.
- Thorough histories, physicals, and diagnostic...
The enigma of endocrinological diagnoses

workups.

• An exceptional physician-patient relationship.

Grouping of symptoms into a diagnosis is not an exact science but rather requires some of the art of medicine which can recognize variableness of disease presentation within a population of interest. Harvey Cushing's recognition of these lessons warrants remembrance of his name not only in the context of hypercortisolism, but as an example of how we should strive to practice medicine.

References

Management of hyperlipidemia in patients with statin intolerance

Kareem Jamani (Meds 2010)
Faculty reviewer: Dr. Tisha Joy, Department of Medicine, UWO

Why statins?

Statins, or HMG CoA reductase inhibitors, are among the most commonly prescribed drugs in the world today. These medications have been repeatedly shown to reduce low-density lipoprotein cholesterol (LDL-C) by 19-60% depending on the statin and dose used. In patients with existing coronary artery disease (CAD), statins have been shown to decrease incidence of non-fatal myocardial infarction, incidence of stroke, mortality from CAD, and all-cause mortality. These same benefits have also been found in patients without CAD but with cardiovascular risk factors including diabetes. For this reason, statins are considered to be first line in the management of hyperlipidemia in patients who, according to the Framingham risk calculator, are at high risk for coronary artery disease as well as those at medium or low risk who have failed to meet lipid targets with lifestyle modification.

Adverse effects and statin intolerance

Despite the significant effect of these drugs on mortality and morbidity, statins, like all drugs, have adverse effects. However, the HMG CoA reductase inhibitors generally have a favorable side-effect profile. The most common adverse effects and the primary contributors to statin-intolerance are muscle symptoms and creatine kinase (CK) elevations.

There are many definitions in the literature regarding the spectrum of statin-induced muscle symptoms. One commonly used set of definitions, from the National Lipid Association (NLA) Statin Safety Assessment Task Force, is as follows: (1) myalgia: muscle pain or soreness, (2) myopathy: myalgias, weakness or cramps and CK >10X the upper limit of normal, and (3) rhabdomyolysis: CK >10 000 IU/L or CK >10X the upper limit of normal plus elevation of serum creatinine or need for intravenous hydration. The rate of statin-induced myalgia in observational studies is 10-15% while the rate of myopathy is 0.1-0.2%. Meanwhile, rhabdomyolysis is even less common and has been seen mainly when statins have been used in combination with fibrates or cyclosporine.

In the case of myopathy or rhabdomyolysis, the NLA task force recommends discontinuing the statin. Restarting the statin after these events is controversial; nevertheless, there is a general consensus that the clinician must weigh the risks and benefits before making this decision. However, most patients on a statin presenting with muscle symptoms will fit the definition of myalgia. If these myalgias are intolerable, the NLA recommends discontinuing the statin. Meanwhile, if the myalgias are tolerable, the statin should be continued at the same or lower dose or a statin holiday may be given.

When patients have recurrent myalgias after taking a reduced dose of their statin or after restarting their statin subsequent to a drug holiday, alternative approaches to lipid management are required. This presents a challenge to physicians managing lipids in patients with or at risk for vascular disease because non-statin lipid lowering medications have not been shown to have the same robust effect on morbidity and mortality as statins and present their own set of adverse effects. In the recent literature, alternative statin regimens aimed at those who have previously been intolerant to the medications have been proposed. Three such regimens are reviewed below.

Modified statin therapy

Switching the statin

According to the Prediction of Muscular Risk in Observational Conditions (PRIMO) study, an observational trial of nearly 8000 unselected patients using statins in France, high dose fluvastatin (60mg) is associated with the lowest rate of muscular symptoms (5.1%) when compared to high dose pravastatin (10.9%), atorvastatin (14.9%) and simvastatin (18.2%). This had led many clinicians to recommend a trial of switching patients intolerant to their current statin to fluvastatin. While this statin is considered to be lower in potency than others, a recent trial showed fluvastatin 60mg reduced LDL-C by 31% and significantly reduced atherosclerotic plaque volume in patients with CAD. Furthermore, fluvastatin XL has been demonstrated to be well-tolerated among statin-intolerant patients.

Alternate day and weekly statin dosing

Given that atorvastatin and rosuvastatin have long half-lives, alternate day dosing of these statins has recently been attempted in statin intolerant patients to reduce the risk of adverse muscular effects. While tolerated by 72% of patients, a dose of 2.5-10mg of rosuvastatin every other day in previously statin-intolerant patients has been found to reduce LDL-C by 34%. Similarly, a 23% reduction in LDL-C has been reported in 74% of previously intolerant patients now receiving once weekly rosuvastatin. However, these studies have not yet addressed whether alternate day or weekly statin dosing has the same effect on vascular event rates and mortality rates that daily dosing does.

Statin and ezetimibe combination

Ezetimibe is a cholesterol absorption inhibitor that has received a significant amount of attention since a double-
Management of hyperlipidemia in patients with statin intolerance

blind study showed similar LDL-C reductions between ezetimibe (10mg/day) combined with atorvastatin 10mg/day and atorvastatin 80mg/day alone. However, even with the lower dose of statin in this short trial, the combination therapy did not have a lower rate of musculoskeletal side-effects and CK elevations than the high dose statin therapy. Further, in a more recent long-term (48 week) trial comparing the safety of ezetimibe combined with simvastatin and simvastatin alone, there was no difference in musculoskeletal adverse-effects or CK levels. However, a recent randomized controlled trial has revealed that the combination of fluvastatin and ezetimibe is well-tolerated in statin-intolerant patients.

Non-statin therapy

When patients with hyperlipidemia cannot tolerate any form of statin therapy, non-statin alternatives can be employed. These include fibrates, niacin, bile acid absorption inhibitors, ezetimibe, and potentially omega-3 fatty acids.

Niacin

Niacin is perhaps the most potent of these drugs and has been shown to raise high-density lipoprotein cholesterol (HDL-C) and lower LDL-C as well as, in older studies, to reduce cardiovascular events and mortality. However, the side effects, which include cutaneous flushing and gastrointestinal upset, have limited its use. Recently, there has been renewed interest in niacin, including ongoing trials evaluating mortality outcomes and investigation into attenuation of these side-effects.

Fibrates

Fibrates are well studied and have been found to significantly reduce triglyceride levels and increase HDL-C levels while having a smaller effect in reducing LDL-C levels. In terms of outcomes, two recent meta-analyses found that while currently available fibrates significantly reduce the odds of non-fatal myocardial infarction (MI), they had no effect on cardiovascular mortality, rate of stroke, or all-cause mortality. Adverse effects in both of these trials were primarily gastrointestinal, while myalgias occurred at the same rate as in the placebo groups.

Bile acid and cholesterol absorption inhibitors

Bile acid absorption inhibitors, similar to niacin, have been studied mostly in older, pre-statin era trials. In these trials, cholestyramine, a first generation bile acid sequestrant, mainly reduced LDL-C levels as well as cardiovascular events and mortality. However, again like niacin, these drugs have been limited by their gastrointestinal side-effects such as constipation. A newer bile acid sequestrant, colesevelam, is tolerated much better by patients and delivers similar LDL-C reductions as the older medications, but no outcome data are available to this point. Ezetimibe alone has been shown to deliver modest reductions in LDL-C and, in two trials, has been well tolerated by patients intolerant to statins. However, there is currently no evidence that this drug influences cardiovascular event or mortality rates.

Omega-3 fatty acids

Recently, there has been some interest in the role of omega-3 fatty acids in cardiovascular disease. A large (18000 patients), randomized trial in Japan found that omega-3 supplementation (eicosapentaenoic acid 1800mg/day) significantly reduced triglyceride levels as well as non-fatal coronary events. However, we await replication of these findings in randomized double-blind, placebo-controlled settings. Adverse effects have included gastrointestinal disturbance, skin reactions, and hemorrhage.

Conclusion

Statins have been widely studied and there is robust evidence supporting their lipid lowering properties and beneficial effects on cardiovascular morbidity and mortality. These medications are generally safe and serious adverse events are rare. However, the most common side-effects that lead to statin-intolerance are muscle symptoms. When patients are unable to tolerate their current statin, there is some evidence to support switching to fluvastatin, less frequent statin dosing, or combination with ezetimibe. However, it is currently unclear if the mortality benefits associated with statins carry over to these modified statin therapies. If patients are unable to tolerate any form of statin therapy, non-statin medications may be used. Unfortunately, many of them are not well tolerated and are still awaiting convincing data for cardiovascular event benefit. Further investigation into the efficacy on cardiovascular outcomes in alternate statin and non-statin regimens in statin-intolerant patients is required. While medications for hyperlipidemia may be tailored according to adverse effects experienced by patients as well as their particular lipid profile, it is important to continually emphasize the need for lifestyle modification including diet and exercise in the management of hyperlipidemia.

References

3. Brugts JJ, Yetgin T, Hoeks SE, et al. The benefit of statins in people without established cardiovascular


Cystic fibrosis-related diabetes

Kathryn McIntyre (Meds 2012)
Faculty reviewer: Dr. Charlotte McDonald, Department of Medicine, UWO

Background

Cystic fibrosis (CF) is an autosomal recessive disease that occurs in one of every 3600 births in Canada.\(^1\) It is caused by a mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene which encodes a chloride ion channel. Derangement in chloride transport results in dysfunction of multiple organ systems, most notably the lungs. Characterized by progressive obstructive lung disease, the clinical course of CF is one of chronic and recurrent pulmonary infections leading to inflammation and remodeling of the airways. In addition to lung disease, the majority of patients also exhibit malabsorption secondary to exocrine pancreatic insufficiency. Whereas lung disease and pancreatic insufficiency typically manifest in infancy, certain complications tend to occur later in the course of the disease. Cystic fibrosis-related diabetes (CFRD) is a feature of CF that occurs in many patients as they reach adulthood. CFRD was unheard of half a century ago when CF was almost uniformly fatal in early childhood. However, as the median survival age has steadily increased, to where it approaches 40 today, this later onset complication is becoming increasingly prevalent. Only 2% of children with CF have CFRD but that increases to 20% of adolescents and half of adults above the age 30.\(^3\) Not only is the development of diabetes an added burden to a patient population that already faces a complex daily treatment regimen, it is associated with a decline in pulmonary function and a decrease in life expectancy.\(^4 \cdot 5\)

Pathophysiology

Although CFRD shares certain characteristics with both type 1 diabetes and type 2 diabetes, it is a separate entity with a unique pathophysiology. As in type 1 diabetes, insulin deficiency is the primary defect but this is usually relative rather than absolute. Similar to type 2 diabetes the onset of CFRD is usually gradual and insidious. CFRD is classified under other types of diabetes, falling into the category of diabetes secondary to disease of the exocrine pancreas.\(^6\) In CF, absent or aberrant function of the CFTR chloride channel on the pancreatic ducts leads to increased viscosity of digestive secretions.\(^7\) The viscous secretions obstruct the pancreatic ducts leading to progressive fibrosis and fatty infiltration of the pancreas. As a result there is a decrease in the number of islets as well as structural disorganization of remaining islets leading to loss of β-cell function.\(^8 \cdot 9\)

Loss of β-cell function is a gradual process and patients pass through a continuum from normal glucose tolerance to impaired glucose tolerance and eventually diabetes. Impaired insulin secretion is seen in patients before the onset of CFRD, with alterations in the kinetics of insulin secretion occurring early in the disease process. Patients with CF without impaired glucose tolerance exhibit a decrease in peak insulin concentration and a delay in reaching peak insulin despite having normal glucose tolerance.\(^10 \cdot 11\) As β-cell function continues to deteriorate, patients show decreasing insulin concentrations and higher plasma glucose concentrations following an oral glucose load, eventually crossing the threshold into diabetes.\(^12 \cdot 13\)

Because the destructive process is not specific for β-cells, there is also damage to other cell types of the islets and patients with CFRD show impaired secretion of glucagon and pancreatic polypeptide.\(^13\) There is evidence of a relative increase in somatostatin secretion, which could further decrease insulin and glucagon release.\(^8 \cdot 14\)

The role of peripheral insulin resistance in CFRD is not clear and the insulin sensitivity of patients is variously reported as normal, decreased, or even increased. Overall, there is insufficient evidence that insulin resistance plays a major role in the pathogenesis of CFRD and whatever effect it does have is certainly small in comparison to β-cell dysfunction.\(^15 \cdot 16\) Regardless of the overall role of insulin resistance in the pathophysiology of CFRD, there are circumstances in which patients will experience at least transient insulin resistance. Exacerbations of lung disease and use of glucocorticoids are frequent occurrences for CF patients. These situations lead to a decrease in insulin sensitivity resulting in a sharp increase in insulin requirements.\(^17\)

Diagnosis and management

Diagnosis of CFRD is not straightforward due to the fluctuating health status of CF patients. Transient dysfunction of glucose metabolism is frequent during disease exacerbations and as such measures of glucose metabolism must be interpreted in the context of the patient's current health.\(^18\) The diagnostic criteria for CFRD are similar to that for type 1 and type 2 diabetes except that in CFRD there is a further subdivision of patients depending on whether or not they exhibit fasting hyperglycemia.\(^19\)

Patients with CFRD are often asymptomatic at diagnosis,\(^20\) which necessitates periodic screening of CF patients for derangements in glucose metabolism. Although fasting plasma glucose (FPG) is the recommended screening test for diabetes,\(^21\) its use in screening for CFRD is not ideal. The use of FPG as a screening test will fail to identify the large proportion of patients who have CFRD without fasting hyperglycemia. Because an oral glucose tolerance test (OGTT) can identify patients with CFRD without fasting hyperglycemia, it is a much more sensitive test. Given that CFRD tends to develop in the adolescent or early adult period, annual OGTT screening beginning in early adoles-
Cystic fibrosis-related diabetes

ence is a rational approach used in many centres to ensure that patients with CFRD are identified early.18,22,23

In patients diagnosed with CFRD with fasting hyperglycaemia, insulin therapy is indicated. Because many patients with CF have a variable appetite and meal schedule due to frequent illness, a basal-bolus insulin regimen provides needed flexibility.24 Both nutritional status and pulmonary function have been found to improve following the induction of insulin therapy.25 Currently, the best treatment for patients who have CFRD without fasting hyperglycaemia is not clear. CFRD without fasting hyperglycaemia has not been associated with acute or chronic complications of diabetes; therefore, patients are often not started on insulin therapy unless they have symptoms of hyperglycaemia.19,26 However, because the CFRD associated decline in nutritional status and pulmonary function usually precedes the onset of fasting hyperglycaemia, it may be beneficial to begin insulin therapy at an earlier stage.27 Observational studies have noted an increase in BMI and improved measures of pulmonary function following the initiation of insulin therapy in patients without fasting hyperglycaemia.25,28 However, the only randomized, placebo-controlled trial to date found that although insulin therapy improved BMI in patients with CFRD without fasting hyperglycaemia, there was no effect on pulmonary function or frequency of lung disease exacerbations.29 The potential benefits of initiating treatment in patients prior to the development of fasting hyperglycaemia must be weighed against the concern that insulin therapy will further complicate the already demanding day-to-day self care to which a CF patient must adhere.

Patients with CFRD are at risk of a subset of the acute and chronic complications that occur in patients with type 1 diabetes and type 2 diabetes. Because the pathophysiology of CFRD results in glucagon deficiency in combination with residual endogenous insulin secretion, diabetic ketoacidosis is unexpected, and in fact has only rarely been reported.30,31 As in all patients treated with insulin, hypoglycaemia is a treatment related concern. Despite glucagon deficiency, patients with CFRD have not shown an increased propensity for severe hypoglycaemic episodes, as they are able to generate a sufficient adrenergic response to hypoglycaemia.32 Chronically, patients with CFRD are at risk of developing the microvascular complications of diabetes. In patients who have had CFRD with fasting hyperglycaemia for at least ten years, rates of peripheral neuropathy and diabetic retinopathy occur at a frequency that approaches that seen in patients who have had type 1 diabetes for a similar duration; however, the severity of both complications tends to be milder in CFRD.26,32 There is a high prevalence of microalbuminuria in patients with CFRD but progression to renal failure is rare.26 Screening for diabetic nephropathy is complicated by the fact that many CF patients regularly take medications known to be nephrotoxic and so the cause of the high frequency of microalbuminuria may be due to factors other than diabetes.26,34 Patients with CFRD do not appear to be at risk for the macrovascular complications of diabetes, presumably because of the low frequency of hypertension and dyslipidemia in the CF population.35

Due to the decreased life expectancy of patients with CFRD in comparison to CF patients without diabetes, the development of CFRD has generally been regarded as a poor prognostic indicator. However, the gap between the median survival age of CF patients with and without CFRD is beginning to narrow. Earlier diagnosis and treatment has been credited with this improved outlook.3 This suggests that routine screening and early initiation of insulin therapy to achieve tight glycemic control may be important to prevent the development of microvascular complications during the longer survival period. However, there is a lack of randomized trials investigating the impacts of diagnostic and treatment strategies. Despite the increased life expectancy that advances in medical care have afforded patients, CF remains a fatal disease. As patients approach end of life, the goals of CFRD treatment should presumably transition to controlling hyperglycemic symptoms while minimizing the burden of treatment.

References

Cystic fibrosis-related diabetes


Prescribing Summary

**Patient Selection Criteria**

THERAPEUTIC CLASSIFICATION: Antidiabetic Agent: Long-acting Recombinant Human Insulin Analogue

INDICATIONS AND CLINICAL USE

LANTUS (insulin glargine injection [rDNA origin]) is a novel recombinant human insulin analogue indicated for once-daily subcutaneous administration in the treatment of patients over 17 years of age with Type 1 or Type 2 diabetes mellitus who require basal (long-acting) insulin for the control of hyperglycemia. LANTUS is also indicated in the treatment of pediatric patients with Type 1 diabetes mellitus who require basal (long-acting) insulin for the control of hyperglycemia.

CONTRAINDICATIONS

LANTUS (insulin glargine injection [rDNA origin]) is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. (For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING sections of the Product Monograph.)

SPECIAL POPULATIONS

Pregnant Women: Teratogenic effects: Patients with diabetes should be advised to inform their doctor if they are pregnant or are contemplating pregnancy. There are no well-controlled clinical studies of the use of insulin glargine in pregnant women. Only a limited number of pregnancies were exposed during Post Marketing Surveillance with insulin glargine. As with other insulins, adverse pregnancy outcomes did not indicate any trends suggesting a link to insulin glargine. Insulin requirements may decrease during the first trimester, generally increase during the second and third trimesters, and rapidly decline after delivery. Careful monitoring of glucose control is essential in such patients.

Nursing Women: It is unknown whether insulin glargine is excreted in significant amounts in human milk. Caution should be exercised when LANTUS is administered to a nursing woman. Lactating women may require adjustments in insulin dose and diet.

Pediatrics (<6 years of age): Safety and effectiveness of LANTUS have been established in children over 6 years of age with Type 1 diabetes mellitus.

Geriatrics (>45 years of age): In clinical studies, the only difference in the elderly subpopulation compared to the entire study population was an expected higher incidence of cardiovascular events in both insulin glargine and NPH human insulin-treated patients. Hypoglycemia may be difficult to recognize in the elderly. The initial dose, dose increments, and maintenance dosage should be conservative to avoid hypoglycemic reactions. Progressive deterioration of renal function may lead to steady decrease in insulin requirements. Careful glucose monitoring and dose adjustments of insulin or insulin analogues including LANTUS may be necessary.

Safety Information

WARNINGS

Hypoglycemia is the most common adverse effect of insulin, including LANTUS. As with all insulins, the timing of hypoglycemia may differ among various insulin formulations. Glucose monitoring is recommended for all patients with diabetes.

Any change of insulin should be made cautiously and as long as it is administered at the same time every day.

Hypoglycemia may occur if the insulin dose is too high in relation to the insulin requirement (see Hypoglycemia section below). The use of too low insulin dosages or discontinuation of treatment, especially in Type 1 diabetes, may lead to hypoglycemia and diabetic ketoacidosis. Uncorrected hypoglycemic or hyperglycemic reactions can cause loss of consciousness, coma, or death.

Hypoglycemia: As with all insulin preparations, hypoglycemic reaction, especially during initiation of therapy, may be associated with the administration of LANTUS. Hypoglycemia is the most common adverse effect of insulins. Early warning symptoms of hypoglycemia may be different, be less pronounced or absent under certain conditions, as for example, in patients whose glycemic control is markedly improved, in elderly patients, in patients where an autonomic neuropathy is present, in patients whose hypoglycemia is developing gradually, in patients with a long history of diabetes, in patients with psychologic illness, or in patients receiving concurrent treatment with certain other drugs such as beta-blockers. Hypoglycemia may occur with other substances including alcohol and psychiatric medications, street drugs, birth control pills, injections and patches (see DRUG INTERACTIONS, Drug-Drug Interactions). Such situations may result in severe hypoglycemia (and possibly, loss of consciousness) prior to patients’ awareness of hypoglycemia.

The time of occurrence of hypoglycemia depends on the action profile of the insulins used and may, therefore, change when the treatment regimen or timing of administration is changed.

As with all insulins, additional caution (including intensified blood glucose monitoring) should be exercised in patient populations who are at greater risk for clinically significant sequelae from hypoglycemic episodes.

Injection Site and Allergic Reactions: As with any insulin therapy, lipodystrophy may occur at the injection site and delay insulin absorption. Other injection site reactions with insulin therapy include redness, pain, itching, hives, swelling, and inflammation. Continuous rotation of the injection site within a given area may help to reduce or prevent these reactions. Minor mirror reactions to insulin usually resolve in a few days to a few weeks.

Immediate-type allergic reactions are rare. Such reactions to insulin (including insulin glargine) or the excipients may, for example, be associated with generalized skin reactions, angioedema, bronchospasm, hypotension, or shock and may be life-threatening.

ADVERSE REACTION SERIOUSNESS AND INCIDENCE (see full listing)

Type 1 and Type 2 Diabetes in Adults: The adverse events most commonly associated with LANTUS (insulin glargine injection [rDNA origin]) include the following: Body as a whole: allergic reaction; Hypoglycemia: Skin and appendages: Injection site reaction, lipodystrophy, pruritus, and rash; Other: antibodies formation, Eyes: A marked change in glycemic control may cause temporary visual impairment, due to temporary alteration in the pupillary and refractive index of the lens.

Type 1 Diabetes in Children and Adolescents: Study 3003: The most commonly reported event was lipodystrophy, a known consequence of insulin injections. The intensity was mostly mild. Injection site events were assessed as possibly related in 9 (6.2%) LANTUS subjects and 3 (2.9%) human NPH subjects. However, none of these subjects discontinued due to these events.

Study 3013: Extension of Study 3003, uncontrolled long-term follow-up study of 143 patients who were well controlled on LANTUS from Study 3003, for 201–1159 days. The most common adverse events were upper respiratory infections, infection, and rhinitis. Note that when comparing safety findings between studies, the difference in length of exposure needs to be kept in mind.

Study 4005: Controlled, randomized, double-crossover; 26 subjects age range 12–20, regimen of LANTUS + lispro vs. human NPH + human regular. Adverse events were equally distributed between the two treatment regimens. The most common adverse events were upper respiratory infections, infection, and rhinitis. Note that when comparing safety findings between studies, the difference in length of exposure needs to be kept in mind.

To report an adverse event, contact Canada Vigilance by toll-free telephone: 1.866.224.4234, toll-free fax: 1.866.678.6769; online: www.healthcanada.gc.ca/medeffect, or email: CanadaVigilance@HC-sc.gc.ca; or contact sanofi-aventis Canada Inc., Laval, Quebec. H7L 4A8, at 1.888.652.6687.

Administration

Dosing Considerations: LANTUS (insulin glargine injection [rDNA origin]) is a novel recombinant human insulin analogue. Its potency is approximately the same as human insulin. It exhibits a glucose-lowering profile with no pronounced peak with a prolonged duration of action that permits once-daily basal dosing. LANTUS is administered subcutaneously once a day. It may be administered at any time during the day as long as it is administered at the same time every day.

The desired blood glucose levels as well as the doses and timing of antidiabetic medications must be determined and adjusted individually.

Dose adjustment may be required, for example, if the patient’s timing of administration, weight or lifestyle changes or other circumstances arise that increase susceptibility to hypoglycemia or hyperglycemia (see WARNINGS and PRECAUTIONS, Hypoglycemia). The dose may also have to be adjusted during intercurrent illness (see WARNINGS and PRECAUTIONS, Intercurrent Conditions). Any change in insulin dose should be made under medical supervision.

The prolonged duration of activity of LANTUS is dependent on injection into subcutaneous space. LANTUS is not intended for intravenous or intramuscular administration. Intravenous administration of the usual subcutaneous dose could result in severe hypoglycemia.
Recommended Dose and Dosage Adjustment: Initiation of LANTUS therapy in clinical studies with insulin-naive patients with Type 2 diabetes, LANTUS was started at a dose of 10 U once daily, and subsequently adjusted according to the patient's needs (see CLINICAL TRIALS section of the Product Monograph).

Changeover to LANTUS: When changing from a treatment regimen with an intermediate or long-acting insulin to a regimen with LANTUS, the amount and timing of short-acting insulin or fast-acting insulin analogue or the dose of any oral antidiabetic drug may need to be adjusted secondary to the risk of hypoglycemia. In clinical studies when patients were transferred from once-daily NPH human insulin or ultralente human insulin to once-daily LANTUS, the initial dose was usually not changed. However, in studies when patients were transferred from twice-daily NPH human insulin to LANTUS once daily, the initial dose (4 U) was usually reduced by approximately 20% (compared to total daily U of NPH human insulin) and then adjusted based on patient response.

A program of close metabolic monitoring under medical supervision is recommended during transfer and in the initial weeks thereafter. The amount and timing of short-acting insulin or fast-acting insulin analogue may need to be adjusted. This is particularly true for patients with acquired antibodies to human insulin needing high-dose insulin doses and occurs with insulin analogues. Such patients may experience a greater insulin response to LANTUS.

With improved metabolic control and resulting increase in insulin sensitivity, further adjustment of the dose of LANTUS and other insulins or oral antidiabetic drugs in the regimen may become necessary.

Administration: LANTUS is administered by subcutaneous injection. The injection area must not be rubbed.

As with all insulins, injection sites within an injection area (abdomen, thigh or deltoid) must be alternated from one injection to the next. Patients should be rigorous with site rotation secondary to prolonged depo-injection. In clinical studies, there was no relevant difference in insulin glargine absorption after abdominal, deltoid, or thigh subcutaneous administration. As for all insulins, the rate of absorption, and consequently the onset and duration of action, may be affected by exercise and other variables.

Preparation and Handling: LANTUS is a clear solution, not a suspension.

Parenteral drug products should be inspected visually prior to administration whenever the solution and the container permit. LANTUS must only be used if the solution is clear and colourless with no particles visible. To minimize local irritation at the injection site, it is recommended to allow the insulin to reach room temperature before injection.

Cartridge version only: If the injection pen malfunctions, LANTUS may be drawn from the cartridge into a U 100 syringe and injected. A new sterile syringe must be used.

Mixing and Diluting: LANTUS must not be mixed with any other insulin. Mixing can change the time/peak profile of LANTUS and cause precipitation.

LANTUS must not be diluted. Diluting can change the time/peak profile of LANTUS.

LANTUS (insulin glargine (rDNA origin) "100 units/ml (U/100) is available in the following package sizes:

- 10-mL vials
- 2 (10) vials
- 3 mL Sol SST® (pre-filled disposable pen), package of 5.

Table 1. Adverse Events by Body System (% Reported in Study 3093.01 Percent Incidence)

<table>
<thead>
<tr>
<th>Adverse Event (Diagnosis)</th>
<th>Body System/Coded Term</th>
<th>Number of Subjects</th>
<th>Human NPH</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Body as a whole</strong></td>
<td><strong>Injection</strong></td>
<td>2 (10.8)</td>
<td>3 (17.7)</td>
</tr>
<tr>
<td></td>
<td><strong>Application site</strong></td>
<td>2 (10.8)</td>
<td>3 (17.7)</td>
</tr>
<tr>
<td></td>
<td><strong>Abdominal pain</strong></td>
<td>2 (10.8)</td>
<td>3 (17.7)</td>
</tr>
<tr>
<td></td>
<td><strong>Anaphylactic reaction</strong></td>
<td>2 (10.8)</td>
<td>3 (17.7)</td>
</tr>
<tr>
<td></td>
<td><strong>Hypersensitivity</strong></td>
<td>2 (10.8)</td>
<td>3 (17.7)</td>
</tr>
<tr>
<td></td>
<td><strong>Intraocular pressure</strong></td>
<td>2 (10.8)</td>
<td>3 (17.7)</td>
</tr>
<tr>
<td></td>
<td><strong>Intraocular pain</strong></td>
<td>2 (10.8)</td>
<td>3 (17.7)</td>
</tr>
<tr>
<td></td>
<td><strong>Inflammation</strong></td>
<td>2 (10.8)</td>
<td>3 (17.7)</td>
</tr>
<tr>
<td></td>
<td><strong>Infection</strong></td>
<td>2 (10.8)</td>
<td>3 (17.7)</td>
</tr>
<tr>
<td></td>
<td><strong>Laryngitis</strong></td>
<td>2 (10.8)</td>
<td>3 (17.7)</td>
</tr>
<tr>
<td></td>
<td><strong>Nasal congestion</strong></td>
<td>2 (10.8)</td>
<td>3 (17.7)</td>
</tr>
<tr>
<td></td>
<td><strong>Rhinitis</strong></td>
<td>2 (10.8)</td>
<td>3 (17.7)</td>
</tr>
<tr>
<td></td>
<td><strong>Sinusitis</strong></td>
<td>2 (10.8)</td>
<td>3 (17.7)</td>
</tr>
<tr>
<td></td>
<td><strong>Skin and subcutaneous</strong></td>
<td>3 (17.7)</td>
<td>3 (17.7)</td>
</tr>
<tr>
<td></td>
<td><strong>Sinusitis</strong></td>
<td>2 (10.8)</td>
<td>3 (17.7)</td>
</tr>
<tr>
<td></td>
<td><strong>Sinusitis and rhinitis</strong></td>
<td>2 (10.8)</td>
<td>3 (17.7)</td>
</tr>
<tr>
<td></td>
<td><strong>Sinusitis and loss of smell</strong></td>
<td>2 (10.8)</td>
<td>3 (17.7)</td>
</tr>
<tr>
<td></td>
<td><strong>Sinusitis and rhinitis</strong></td>
<td>2 (10.8)</td>
<td>3 (17.7)</td>
</tr>
<tr>
<td></td>
<td><strong>Sinusitis and loss of smell</strong></td>
<td>2 (10.8)</td>
<td>3 (17.7)</td>
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<tr>
<td></td>
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<td></td>
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</tr>
<tr>
<td></td>
<td><strong>Skin and subcutaneous</strong></td>
<td>3 (17.7)</td>
<td>3 (17.7)</td>
</tr>
</tbody>
</table>

Supplemental Product Information

PRECAUTIONS

Hepatic/Biliary/Pancreatic: Although studies have not been performed in patients with diabetes and hepatic impairment, LANTUS requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism.

Inflammation: insulin administration may cause insulin antibodies to form. In clinical studies, antibodies that cross-react with human insulin and insulin glargine were observed in both NPH human insulin and insulin glargine treatment groups with similar percentages of incidence and decreased titres. There was no correlation in either treatment group between increases or decreases in these antibodies and changes in either A1C or total insulin requirements. In theory, the presence of such insulin antibodies may necessitate adjustment of the insulin dose in order to correct a tendency to hyperglycemia or hypoglycemia, but has not been found on review of LANTUS clinical trials and available post-marketing data.

Infusion Conditions: Insulin requirements may be altered during intravenous conditions such as infection or injury, emotional disturbances, or diet.

Renal: Although studies have not been performed in patients with diabetes and renal impairment, LANTUS requirements may be diminished due to reduced insulin metabolism. Careful glucose monitoring and close adjustments of insulin or insulin analogues including LANTUS must be necessary in patients with renal dysfunction.

As with all insulin preparations, the time course of LANTUS action may vary in different individuals or at different times in the same individual and the rate of absorption is dependent on blood supply, temperature, and physical activity.

Insulins may cause sodium retention and edema; particularly if previously poor metabolic control is improved by insulin therapy. Patients with human insulin analogues may be hyperosmolar to other insulins, with a risk of hypoglycemia and/or cross-reactivity. In a clinical study of hypoosmolar and hyperglycemic regulatory hormone responses were similar after intravenous insulin glargine and regular human insulin both in healthy subjects and adult patients with Type 1 diabetes.

When LANTUS and regular human insulin were mixed immediately before injection in dogs, a delayed onset of action and time to maximum effect for regular human insulin was observed. The total bioavailability of the insulin was also slightly decreased compared to separate injections of LANTUS and regular human insulin. The relevance of these observations in dogs is not known to humans.

ADVERSE REACTIONS

Adverse events that occurred in a pediatric controlled trial in at least 1% of patients treated with LANTUS are shown in Table 1.
Hypoglycemia may occur if the insulin dose is too high in relation to the insulin requirement (see Hypoglycemia section). The use of too low insulin dosages or inadequate glucose control requires adjustments in insulin dose and diet.

Careful monitoring of glucose control is essential. Patients with diabetes must inform their doctor if they are pregnant or are contemplating pregnancy.

Nursing Women:
It is unknown whether APIDRA™ is excreted in human milk. Many drugs, including human insulin, are excreted in human milk. For this reason, caution should be exercised when APIDRA™ is administered to a nursing woman. Lactating women may require adjustments in insulin dose and diet.

Pediatrics:
Safety and effectiveness of APIDRA™ in pediatric patients have not been established.

Geriatrics (> 65 years of age):
Hypoglycemia may be difficult to recognize in the elderly. In Phase III clinical trials (n=2,408), APIDRA™ was administered to 147 patients > 65 years of age and 27 patients > 75 years of age. The majority of these were patients with Type 2 diabetes. The change in glycated hemoglobin (A1C) values and hypoglycemia frequencies did not differ by age, but greater sensitivity of some older individuals cannot be ruled out.

Discontinuation of treatment, especially in Type 1 diabetes, may lead to hyperglycemia and diabetic ketoacidosis. Uncorrected hyperglycemic or hyperglycemic reactions can cause loss of consciousness, coma, or death. Any change of insulin should be made cautiously and only under medical supervision. As with other insulins, additional caution should be exercised in patients with a long history of diabetes on insulin who might be prone to develop hypoglycemia and in patients with a previous history of cardiac, ischemic disorders who might be prone to develop cardiac adverse events. Changes in insulin strength, manufacturer, type (e.g., regular, NPH, or insulin analogues), or species (animal, human), or method of manufacture (recombinant DNA versus animal-source insulin) may result in the need for a change in dosage. Concomitant oral antidiabetic treatment may need to be adjusted. As with all insulin preparations, the time course of APIDRA™ action may vary in different individuals or at different times in the same individual and is dependent on site of injection, blood supply, temperature, and physical activity. Adjustment of dosage of any insulin may be necessary if patients change their physical activity or their usual meal plan.

Glucose monitoring is recommended for all patients with diabetes.

Hypoglycemia:
As with all insulin preparations, hypoglycemic reactions may be associated with the administration of APIDRA™. Early warning symptoms of hypoglycemia may be different, be less pronounced or absent, under certain conditions, as for example if glycemic control is markedly improved, if hypoglycemia is developing gradually, in elderly patients, in patients with a long history of diabetes, in patients with diabetic nerve disease, in patients using some medications such as beta-blockers, or intensified diabetes control (see DRUG INTERACTIONS). Such situations may result in severe hypoglycemia (and possibly, loss of consciousness) prior to patients' awareness of hypoglycemia.

Severe hypoglycemia may require the assistance of another person. Patients who are unable to take sugar orally or who are unconscious may require an intramuscular/subcutaneous injection of glucagon or should be treated with intravenous administration of glucose by medical personnel. Without immediate medical help, serious reactions or even death could occur.

Hypoglycemia is the most common adverse effect of insulin therapy, including APIDRA™. As with all insulins, the timing of hypoglycemia may differ among various insulin formulations. The time of occurrence of hypoglycemia depends on the action profile of the insulins used and may, therefore, change when treatment regimen is changed.

ADVERSE REACTION SERIOUSNESS AND INCIDENCE (see full listing):
Adverse events commonly associated with human insulin therapy include the following:

Body as a Whole:
Local Allergy:
As with other insulin therapy, local allergy in patients may occur as redness, swelling, or itching at the site of insulin injection. These minor reactions usually resolve in a few days to a few weeks. In some instances, these reactions may be related to factors other than insulin, such as irritants in a skin-cleansing agent or poor injection technique.

Systemic Allergy:
Less common, but potentially more serious, is generalized allergy to insulin, which may cause rash (including pruritus) over the whole body, shortness of breath, wheezing, reduction in blood pressure, rapid pulse, or sweating. Severe cases of generalized allergy, including anaphylactic reactions, may be life-threatening.

Localized reactions and generalized myalgias have been reported with the use of cresol as an injectable excipient.

Hypoglycemia:
Hypoglycemia, a frequent adverse reaction to insulin therapy, may occur if the insulin dose is too high in relation to the insulin requirement. As with all insulins, prolonged or severe hypoglycemic attacks, especially if recurrent, may lead to neurological damage, loss of consciousness, coma, or death.

Skin and Appendages:
As with other insulin therapy, lipodystrophy may occur at the injection site and delay insulin absorption. Continuous rotation of the injection site within a given area may help to reduce or prevent these reactions.

To report an adverse event, contact Canada Vigilance by toll-free telephone: 1-866-234-2345, toll-free fax: 1-866-678-6789, online: www.healthcanada.gc.ca/medeffect, or email: CanadaVigilance@hc-sc.gc.ca; or contact sanofi-aventis Canada Inc., Laval, Quebec H7L 4A8, at 1-888-352-6867.
**Administration**

**Dosage Considerations**

The dosage of APIDRA™ should be individualized and determined based on the physician’s advice in accordance with the needs of the patient. APIDRA™ (insulin glulisine [rDNA origin]) is a recombinant human insulin analogue that has been shown to be equivalent to human insulin. One unit of APIDRA™ has the same glucose-lowering effect as one unit of regular human insulin. After subcutaneous administration it has a more rapid onset and a shorter duration of action.

APIDRA™ should be given by injection within 15 minutes before or within 20 minutes after starting a meal. APIDRA™ should normally be used in regimens that include a longer-acting insulin or basal insulin analogue.

APIDRA™ is intended for subcutaneous administration by injection and for use as a continuous subcutaneous insulin infusion (CSI) in pump systems suitable for insulin infusion.

APIDRA™ should be administered by subcutaneous injection in the abdominal wall, the thigh, or the deltoid, or by continuous subcutaneous infusion in the abdominal wall. As with all insulins, injection sites and infusion sites within an injection area (abdomen, thigh, or deltoid) should be rotated from one injection to the next. As for all insulins, the rate of absorption, and consequently the onset and duration of action, may be affected by injection site, exercise, and other variables. Blood glucose monitoring is recommended for all patients with diabetes.

**Preparation and Handling**

APIDRA™ must only be used if the solution is clear, colourless, with no solid particles visible, and if it is of a water-like consistency. To minimize local irritation at the injection site, it is recommended to allow the insulin to reach room temperature before injection. The instructions for using the APIDRA™ in a pump or with an injection pen must be followed carefully. An empty vial or SoloSTAR® must never be reused and must be properly discarded.

**Vials**

Before withdrawing insulin from the vial for the first time, remove the plastic protective cap. Do not shake the vial vigorously as this may cause frothing. Froth may interfere with the correct measurement of the dose.

**Mixing of Insulin:**

APIDRA™ can be mixed with NPH human insulin (except when administered with pump [see below, Continuous Subcutaneous Insulin Infusion Pump]). If APIDRA™ is mixed with NPH human insulin, APIDRA™ should be drawn into the syringe first. Injection should be made immediately after mixing. No data are available on mixing APIDRA™ with insulin preparations other than NPH human insulin.

Mixtures should not be administered intravenously. Continuous Subcutaneous Insulin Infusion Pump APIDRA™ may be used for continuous subcutaneous insulin infusion (CSI) in pump systems suitable for insulin infusion. When used with an insulin infusion pump, APIDRA™ should not be mixed with any other insulin or diluted with any other solution. Patients using CSI should be comprehensively instructed on the use of the system pump, infusion set and reservoir should be changed every 48 hours using aseptic technique. Patients administering APIDRA™ by CSI must have an alternative insulin delivery system available in case of pump system failure.

**Supplemental Product Information**

**Warnings and Precautions**

Hepatitis/Biliary/Pancreatic Studies (Studies have not been performed in patients with hepatic impairment. APIDRA™ requirements may be diminished due to reduced capacity for glucosopenesis and reduced insulin metabolism, similar to observations found with other insulins. Interruption of CGS infusions may result in loss of effectiveness due to emotional distress, or stress. Insulin Pumps When used as an external insulin pump for subcutaneous infusion, APIDRA™ should not be mixed with any other insulins or diluted with any other solution. Patients using external pump infusion therapy should be trained appropriately. Physicians and patients should carefully evaluate information on pump use in the APIDRA™ Product Monograph, patient insert, and the pump manufacturer’s manual. APIDRA™ specific information should be followed for period of use, frequency of changing infusion sets, or other details specific to APIDRA™ usage; because APIDRA™ specific information may differ from general or other insulin pump manual instructions. Pump or infusion set malfunctions or malfunctions in replacement can lead to hypoglycemia and ketosis in a short time. This is especially pertinent for rapidly acting insulin analogues that are more rapidly absorbed and have a shorter duration of action. Prompt identification and correction of the cause of hypoglycemia or ketosis is necessary; therapy with subcutaneous injection may be required (see ADMINISTRATION. Continuous Subcutaneous Insulin Infusion Pump).

**Risks:**

The pharmacokinetic properties of APIDRA™ were generally maintained in subjects with renal impairment. However, as with all insulins, the requirements for APIDRA™ may be reduced in patients with renal impairment.

**Occupational Hazards:**

The patient’s ability to concentrate and react may be impaired as a result of hypoglycemia or hyperglycemia or, for example, as a result of visual impairment. This may constitute a risk in situations where these abilities are of special importance (e.g., driving a car or operating machinery). Patients should be advised to take precautions to avoid hypoglycemia while driving. It is particularly important in those who have reduced or absent awareness of the warning symptoms of hypoglycemia or have frequent episodes of hypoglycemia. It should be considered whether it is advisable to drive or operate machinery in these circumstances.

---

**Table 1:**

**Number of subjects with at least one episode of symptomatic hypoglycemia in studies Type 1 and Type 2 diabetes**

<table>
<thead>
<tr>
<th>Type 1 Diabetes</th>
<th>Type 2 Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glucose</strong></td>
<td><strong>Comparator</strong></td>
</tr>
<tr>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td><strong>Total episodes</strong></td>
<td>5781883</td>
</tr>
<tr>
<td><strong>Subcutaneous injection</strong></td>
<td>783921</td>
</tr>
<tr>
<td><strong>Continuous Subcutaneous Infusion</strong></td>
<td>2629</td>
</tr>
</tbody>
</table>

---

**Table 2:**

**Common (≥1%) adverse drug reactions in pooled Type 1 and Type 2 studies**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>System Organ Class/ Preferred Form</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse Event</strong></td>
<td><strong>Insulin Glulisine (all studies)</strong></td>
</tr>
<tr>
<td><strong>General Disorders and Administration Site Condition</strong></td>
<td></td>
</tr>
<tr>
<td>Injection site hyperglycemia</td>
<td>9.5</td>
</tr>
<tr>
<td><strong>Metabolism and Nutrition Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Hydroxybutyrate</td>
<td>45.5</td>
</tr>
<tr>
<td>Glucose lowering effect</td>
<td>45.5</td>
</tr>
<tr>
<td><strong>Metabolic System Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Metabolic coma</td>
<td>40.0</td>
</tr>
</tbody>
</table>

---

**Table 3:**

**Established or potential drug-drug interactions**

<table>
<thead>
<tr>
<th>Propranolol</th>
<th>Ref</th>
<th>Effect</th>
<th>Clinical comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral antidiabetic agents</td>
<td>A</td>
<td>May enhance the blood-glucose-lowering effect and increase susceptibility to hypoglycemia</td>
<td>May require closer monitoring of blood glucose level and dose adjustment (reduction) of APIDRA™</td>
</tr>
<tr>
<td>Insulin pumps</td>
<td>B</td>
<td>May reduce the blood-glucose-lowering effect, may enhance or decrease the insulin requirements</td>
<td>May require closer monitoring of blood glucose level and dose adjustment (increase or decrease of APIDRA™)</td>
</tr>
<tr>
<td>Alcohol</td>
<td>C</td>
<td>May either potentiate or weaken the blood-glucose-lowering effect of insulin</td>
<td>May require closer monitoring of blood glucose level and dose adjustment (increase or decrease of APIDRA™)</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>D</td>
<td>The signs of hypoglycemia may be reduced or absent</td>
<td>May require closer monitoring of blood glucose level and dose adjustment (increase or decrease of APIDRA™)</td>
</tr>
</tbody>
</table>

**Legend:**

Legend T - Theoretical

**Drug-food interactions:**

**Drug-Medication interactions:**

**Drug-Behavior interactions:**

**Drug-Lab interactions:**

---

**APIORA**

**Rapid action. Mealtime efficacy.**

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Any change of insulin or human insulin analogue should be made cautiously and all differences should be carefully followed. Hypoglycemia is the most common adverse effect associated with insulins, including the Humalog® (insulin lispro injection) family of insulins. As with other insulin formulations, is dependent upon the individual patient and is for use in conjunction with a longer-acting human insulin, such as Humulin® R except when used in a subcutaneous insulin infusion pump.

CONTRAINDICATIONS

The Humalog® (insulin lispro) family of insulins are contraindicated during episodes of hypoglycemia (for details see SYMPTOMS AND TREATMENT OF OVERDOSE) and in patients sensitive to insulin lispro or any of the excipients they contain.

SPECIAL POPULATIONS

Renal Impairment: Some studies with human insulin have shown increased circulating levels of insulin in patients with renal failure. In a study of 25 patients with type 2 diabetes and varying degrees of renal function (from normal to severe impairment, including endstage renal failure), the pharmacokinetic differences between Humalog® and human regular insulin were generally maintained. However, the sensitivity of the patients to insulin did change, with an increased response to insulin as the renal function declined. Careful glucose monitoring and dose adjustments of insulin, including Humalog®, may be necessary in patients with renal dysfunction.

Hepatic Impairment: Some studies with human insulin have shown increased circulating levels of insulin in patients with hepatic failure. In a study of 22 patients with type 2 diabetes, impaired hepatic function did not affect the subcutaneous absorption or general disposition of Humalog® when compared to patients with no history of hepatic dysfunction. In that study, Humalog® maintained its more rapid absorption and elimination when compared to human regular insulin. Careful glucose monitoring and dose adjustments of insulin, including Humalog®, may be necessary in patients with hepatic dysfunction.

SAFETY INFORMATION

WARNINGS

Due to their quick onset of action, the Humalog® (insulin lispro) family of insulins should be given within 15 minutes before a meal. When necessary, Humalog® (insulin lispro injection) may be given shortly after a meal (within 20 minutes of the start of the meal). When used in a subcutaneous insulin infusion pump, Humalog® should not be diluted or mixed with any other insulin. Patients should carefully read and follow the insulin infusion pump manufacturer’s instructions and the INFORMATION FOR THE PATIENT insert before use.

Hypoglycemia is the most common adverse effect associated with insulins, including the Humalog® family of insulins. As with all insulins, the timing of hypoglycemia may differ among various insulin formulations. Glucose monitoring is recommended for all patients with diabetes.

Any change of insulin or human insulin analogue should be made cautiously and only under medical supervision. Changes in purity, strength, brand (manufacturer), type (insulin lispro, regular, NPH, etc.), species (beef, pork, beef-pork, human), and/or method of manufacture (recombinant DNA versus animal source insulin) may result in the need for a change in dosage.

PRECAUTIONS

General: Humalog® (insulin lispro injection) had a similar safety profile to Humulin® R over the course of the clinical studies although its efficacy has not been studied in clinical trials beyond one year. Humalog® has been shown to control hemoglobin A1C levels as effectively as human insulin in comparator studies specifically designed to study meal-time therapy without optimization of basal insulin regimens. Once a patient is using Humalog®, reassessment and adjustment, as necessary, of the basal insulin regimen (dosage and number of injections) have been shown to optimize overall glycemic control.

ADVERSE REACTIONS

Rarely, administration of insulin subcutaneously can result in lipoatrophy (depression in the skin) or lipo hypertrophy (enlargement or thickening of tissue). Patients should be advised to consult their doctor if they notice any of these conditions. A change in injection technique may help alleviate the problem.

To report any adverse events, please contact Eli Lilly Canada Inc. at 1-888-545-5972.

ADMINISTRATION

DOSEAGE

The dosage of Humalog® (insulin lispro injection), Humalog® Mix25® (25% insulin lispro injection, 75% insulin lispro protamine suspension), and Humalog® Mix50® (50% insulin lispro injection, 50% insulin lispro protamine suspension) are indicated for the treatment of patients with diabetes mellitus who require insulin for the maintenance of normal glucose homeostasis. Humalog® insulins are also indicated for the initial stabilization of diabetes mellitus. Humalog® (insulin lispro injection) is a short-acting insulin analogue and is for use in conjunction with a longer-acting human insulin, such as Humulin® R except when used in a subcutaneous insulin infusion pump.

Although Humalog® insulins have a quicker onset of action and shorter duration of activity, dosing is comparable to regular human insulin. The dosage of a Humalog® insulin, like all other insulin formulations, is dependent upon the individual patient requirements. The dose and number of insulin injections should be adjusted to maintain blood glucose concentrations as close to normal as possible.

Adjustment of dosage may be required in diabetes patients with renal impairment, during intercurrent illness and/or emotional disturbances.

Adjustment of dosage may also be necessary if patients undertake increased physical activity or change their usual diet.

New Patients: Patients receiving insulin for the first time can be started on a Humalog® insulin in the same manner as they would be on animal-source or human insulin.

Patients should be monitored closely during the adjustment period.

Transfer Patients: When transferring patients to a Humalog® insulin, use the same dose and dosage schedule. However, some patients transferring to a Humalog® insulin may require a change in dosage from that used with their previous insulin. Analysis of a database of type 1 diabetic patients indicated that basal insulin requirements increased by 0.04 U/kg, while Humalog® requirements decreased by 0.03 U/kg, after one year of treatment. For type 2 diabetic patients, both short-acting and basal insulin requirements increased slightly after one year of treatment with both Humalog® and Humulin® R.

Optimizing Glycemic Control: In order to achieve optimal glycemic control, changes in total daily dosage, the number of injections per day, and/or timing of injections may be necessary when using a Humalog® insulin.

Once a patient is using Humalog®, reassessment and adjustment, as necessary, of the basal insulin regimen (dosage and number of injections) have been shown to optimize overall glycemic control.

STUDY REFERENCES


SUPPLEMENTAL PRODUCT INFO

THERAPEUTIC CLASSIFICATION

Anti-Diabetic Agent

PHARMACOLOGY

Humalog®

Humalog® (insulin lispro injection) is absorbed more rapidly than regular soluble insulin from s.c. sites of injection and also has a shorter duration of action. Due to its quick onset of action, Humalog® should be given within 15 minutes.
before a meal. When necessary, Humalog® may be given shortly after a meal instead (within 20 minutes of the start of the meal). Small s.c. injected regular insulin typically results in serum insulin concentrations that peak later and remain elevated for a longer time than those following oral use. In healthy volunteers, s.c. regular insulin was given as an absolute reference. Humalog® showed statistically higher peak concentrations (Cmax) which occurred earlier than Humulin® R (Cmax). Total absorption was comparable, with area under the curve (AUC) values of serum concentration vs. time which were not statistically different (see Table 1 and 2). Table 1: Humalog® Pharmacokinetics of Humalog® Compared with Humulin® R in Healthy Volunteers

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Humalog®</th>
<th>Humulin® R</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1/2 (h)</td>
<td>3.6-4.7 h</td>
<td>5.0-7.5 h</td>
</tr>
<tr>
<td>Onset of Action (h)</td>
<td>0.5-0.75 h</td>
<td>0.5-1.0 h</td>
</tr>
<tr>
<td>Time of Maximum Effect (h)</td>
<td>0.75-2 h</td>
<td>0.75-4.5 h</td>
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A) Results predicted from a pharmacokinetic-pharmacodynamic link model.

Subsequent pharmacokinetic studies in type 1 patients confirmed that a significantly faster increase in serum insulin levels and a shorter plasma half life resulted from an injection of Humalog® when compared to Humulin® R (see Figure 1).

**Figure 1: Humalog®**

- **Humalog® R (n=10)**
- **Humulin® R (n=10)** (Mean dose 15.4 U)

| Serum Insulin Conc. (mg/mL) | 0.2 mg/mL
<table>
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<tr>
<td>Time (minutes)</td>
<td>0 60 120 180 240 300 360 420 480</td>
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</table>

Mean Serum Insulin Concentrations in Type 1 Patients Following Injection of Humalog® R and Humulin® R (Basal 0.2 mg/mL in Humulin® Infusions) Postprandial and overall glycemic control

In clinical studies after 1 year, the decrease in glucose excursion during and after meals with Humalog® was consistent, although not always significant, when compared to Humulin® R. However, there was no significant difference in hemoglobin A1C levels between the two treatment groups. These studies were specifically designed to study meal time fluctuation without optimization of basal insulin regimens. Subsequent clinical studies have demonstrated that an intensive insulin treatment regimen with basal insulin optimization, Humalog® controls postprandial glucose and contributes to lower hemoglobin A1C levels to a greater degree than regular human insulin, without increasing the risk of hypoglycemia.

Hypoglycemia

The frequency of hypoglycemia was not statistically significant in 1-year parallel studies Humalog®, n=561, Humulin® R, n=561, but was significantly less with Humalog® therapy in a 6-month crossover study in type 1 patients (n=108) which also demonstrated a significant reduction in nocturnal hypoglycemia with Humalog®.

Use in Pumps

When used in subcutaneous insulin infusion pumps, treatment with Humalog® has been shown to result in lower hemoglobin A1C levels compared to regular human insulin without increasing the risk of hypoglycemia. In clinical trials, that compared Humalog® with regular human insulin, Humalog® consistently showed significantly higher HbA1C improvement in the range of 0.33% to 0.65%.

PRECAUTIONS

Visual disturbances in uncontrolled diabetes due to refractive changes are reversed during the early phase of effective management. However, since alteration in cataract and visual disturbances may not stabilize for a few weeks after initiating therapy, it is wise to postpone prescribing new corrective lenses for 3 to 6 weeks.

Additional adjustment of dosage may be required during intermittent illness and/or emotional disturbances such as stress.

Any rapid- or short-acting insulin formulation should be used with caution in patients with gastroparesis. However, some patients with gastroparesis may benefit from postprandial administration of Humalog® which has been shown to provide postprandial glycemic control similar to that provided by regular insulin.

When using the postprandial dosing approach, the insulin dose can be adjusted according to the actual caloric intake and/or the observed rise in blood glucose following a meal.

Transferring Patients from Other Insulins: Patients taking a Humalog® insulin may require a change in dosage from that used with their usual insulins. If an adjustment is needed, it may occur with the first dose or during the first several weeks or months.

A few patients who have experienced hypoglycemic reactions after transfer from animal-source insulin to human insulin have reported that the early warning symptoms of hypoglycemia were less pronounced or different from those experienced with their previous insulin. However, the counterregulatory and symptomatic (autonomic and neurogenic) responses to hypoglycemia were found and studies were found to be superimposable for insulin lipo and regular human insulin.

Patients whose blood glucose is greatly improved, e.g. by intensified insulin therapy, may lose some or all of the warning symptoms of hypoglycemia and should be advised accordingly. Uncomplicated hypoglycemic or hypoglycemic reactions can result in loss of consciousness, coma or death.

**Renal Impairment:** The requirements for insulin may be reduced in patients with renal impairment.

**Hepatic Impairment:** Although impaired hepatic function does not affect the absorption or disposition of Humalog®, careful glucose monitoring and dose adjustments of insulin, including Humalog®, may be necessary.

**Allergic Reaction:** Prompt recognition and appropriate management of the allergic complications of insulin therapy are important for the safety and effective control of diabetes mellitus. Antibodies to insulin are frequently cross-reactive. Therefore, patients who have demonstrated a specific allergic reaction to other insulins may demonstrate an allergic reaction to a Humalog® insulin. Local allergy in patients occasionally occurs as redness, swelling, and itching at the site of injection. This condition usually resolves in a few days to a few weeks. In some instances, this condition may be related to factors other than insulin, such as irritants in the skin cleansing agent or poor injection technique. Systemic allergy may cause rash (including pruritus) over the whole body, shortness of breath, wheezing, reduction in blood pressure, fast pulse, or sweating. Severe cases of generalized allergy may be life-threatening (see CONTRAINDICATIONS).

**Use in Pregnancy:** Humalog® can be used in pregnancy if clinically indicated. Data on a large number of exposed pregnancies do not indicate any adverse effect of Humalog® on pregnancy or on the health of the fetus/newborn. It is essential to maintain good glucose control in both gestational diabetes and throughout pregnancy in type 1 and type 2 patients. Insulin requirements usually decrease during the first trimester and increase during the second and third trimesters.

Patients with diabetes should be advised to inform their doctor if they are pregnant or are contemplating pregnancy. Careful monitoring of glucose control, as well as general health is essential in pregnant patients with diabetes.

**Nursing Mothers:** The use of Humalog® insulins in nursing mothers has not been studied. Diabetic patients who are nursing may require adjustments in insulin dose and/or diet.

**Pediatric Use:** Clinical trials have been performed in children (61 patients aged 3 to 11 years) and children and adolescents (461 patients aged 9 to 13 years). Humalog®, compared to regular human insulin, showed shorter postprandial glucose levels while maintaining a similar safety profile.

As in adults, Humalog® should be given in 15 minutes before a meal. When necessary, Humalog® may be given shortly after a meal (within 20 minutes of the start of the meal).

The safety and effectiveness of Humalog® Mix50® (52% insulin lispro injection, 75% insulin lispro premixed suspension) and Humalog® Mix50® (52% insulin lispro injection, 50% insulin lispro premixed suspension) in children have not been established.

**Drug Interactions:** Drug interactions with insulin formulations including Humalog® insulins may include the following.

Insulin requirements may be decreased in the presence of agent-such as oral antidiabetic agents, salicylates, sulfon antidiabetics, certain antidepressants (moxonidine oxid compounds), beta adrenergic blockers, alcohol, angiotensin converting enzyme inhibitors and angiotensin II receptor blockers.

Insulin requirements may be increased by medications with hyperglycemic activity such as corticosteroids, insulin, certain lipid-lowering drugs (e.g., nitrates, estrogen, oral contraceptives, phenoxybenzamine, and thyroid replacement therapy).

Hormones that tend to counteract the hypoglycemic effects of insulin include growth hormone, corticotropin, glucocorticoids, thyroid hormone, and glucagon. Epinephrine not only inhibits the secretion of insulin, but also stimulates glucagon secretion. Thus, the presence of such diseases as acromegaly, Cushing's syndrome, hypothyroidism, and pheochromocytoma can complicate the control of diabetes. The hypoglycemic action of insulin may also be antagonized by diphendydramine.

Insulin requirements can be increased, decreased, or unchanged in patients receiving diuretics.

The physician should be consulted when using other medications in addition to a Humalog® insulin.

**SYPHOMENTS AND TREATMENT OF OVERDOSAGE**

With the rapid onset of activity of the Humalog® (insulin lispro) family of insulins, it is important that the insulin analogue be given close to mealtime (within 15 minutes before a meal). When necessary, Humalog® insulin lispro injection may be given shortly after a meal instead (within 20 minutes of the start of the meal). A significant deviation could put the patient at risk of hypoglycemia.

Insulin requires specific overdose definitions because serum glucose concentrations are a result of complex interactions between insulin levels, glucose availability, and other metabolic processes. Hypoglycemia may occur as a result of an excess of insulin or insulin-like relative to food intake and energy expenditure or in patients who have an infection or become ill (typically with diabetes or vomiting).

Symptoms are likely to appear anytime when the blood sugar concentration falls below 3.0 mmol/l (54 mg/dl) but may occur with a sudden drop in blood glucose even when the value remains above 3.0 mmol/l (54 mg/dl). Hypoglycemia may be associated with weakness, confusion, palpitations, dizziness, sweating, and vomiting.

Mild hypoglycemic episodes will respond to oral administration of glucose or sugar containing foods. Correction of moderately severe hypoglycemia can be accomplished by intramuscular or subcutaneous administration of glucagon, followed by oral carbohydrates when the patient recovers sufficiently. Patients who fail to respond to glucagon must be given glucose solution intravenously.

Patients who are unable to take sugar orally or who are unconscious should be treated with intravenous administration of glucose at a medical facility or should be given an injection of glucagon (either intramuscular or subcutaneous). The patient should be given oral carbohydrates as soon as consciousness is recovered.

See Product Monograph for complete prescribing information.

Full Product Monograph is available at www.lilly.ca.

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3600 Carstairs Ave.
Toronto, ON M3J 2E8

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Humalog® Mix25® twice-a-day – basal and mealtime insulin analogues conveniently combined in a single pen – may be just what they have been looking for.

Open the dialogue to Humalog®

Humalog® Mix25® (25% insulin lispro injection, 75% insulin lispro protamine suspension) is indicated for the treatment of patients with diabetes mellitus who require insulin for the maintenance of normal glucose homeostasis. Humalog® insulins are also indicated for the initial stabilization of diabetes mellitus. Humalog® (insulin lispro injection) is a short-acting insulin analogue and is for use in conjunction with a longer-acting human insulin such as Humulin® N except when used in a subcutaneous insulin infusion pump.

The Humalog® family of insulins is contraindicated during episodes of hypoglycemia and in patients sensitive to insulin lispro or any of the excipients they contain. Any change in insulin or human insulin analogue should be made cautiously and only under medical supervision. Mixing of Humalog® with either animal insulins or insulin preparations produced by other manufacturers is not recommended.

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75% insulin lispro protamine suspension

See prescribing summary on page 57
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